THE PATENTS ACT 1970

Section 25(1) read with Rule 55

IN THE MATTER OF:

Patent Application No. 4412/DELNP/2007

IN THE MATTER OF:

Pre-grant representations filed to the grant of patent Under Section 25(1) of the Patents Act 1970 (as amended in 2005), and the patents rules 2005

NOVARTIS AG., Switzerland; - **APPLICANT**

AND

- **OPPONENTS**

(1) Indian Pharmaceutical Alliance dated (Opponent no 1)
(2) Natco Pharma Ltd.(Opponent no 2)
(3) KUMAR SUSHOBHAN (Opponent no 3)
(4) Dr. Reddy's Laboratories Ltd.(Opponent no 4)
(5) Mr. Hiren Darji(Opponent no 5)
(6) G. Srinivasa Rao spiProP at Intellectual Property Solutions(Opponent no 6)
(7) CHIRAG TANNA INK IDEE,(Opponent no 7)
(8) KETAKEE S. DURVE (Opponent no 8)

INTELLECTUAL PROPERTY INDIA
PATENTS DESIGNS TRADE MARKS GEOGRAPHICAL INDICATIONS

Hearing held on 12th, 13th 17th , 18th, 19th May 2021 , 5th August, 2022 , 7th August 2022 and 3rd November 2022

Hearing held on 12th May, 2021

Present on behalf of Applicant:

1. Ms. Archana Shanker , registered Patent Agent.
2. Mr. Devinder Singh Rawat , registered Patent Agent
3. Mamta Jha, (Inttl Advocare)
4.Hemant Singh(Inttl Advocare)

Present on behalf of Opponent:

None appeared

Hearing held on 13th May, 2021

Present on behalf of Applicant :

1. Ms. Archana Shanker , registered Patent Agent.
2. Mr. Devinder Singh Rawat , registered Patent Agent
3. Mamta Jha,
4.Hemant Singh

Present on behalf of Opponent:

1.Mr. S. Majumdar,

2.Ms. Amrita Majumdar,

3.Mr. Dominic Alwaris

Hearing held on 17th May, 2021

Present on behalf of Applicant :

1. Ms. Archana Shanker , registered Patent Agent.
2. Mr. Devinder Singh Rawat , registered Patent Agent
3. Mamta Jha, Inttl Advocare)
4.Hemant (Inttl Advocare)

Present on behalf of Opponent:
1.Ms. Rajeshwari and
2.Ms. Pragya Thakur

Hearing held on 18th May, 2021

Present on behalf of Applicant :

1. Ms. Archana Shanker , registered Patent Agent.
2. Mr. Devinder Singh Rawat , registered Patent Agent
3. Mamta Jha,
4.Hemant Singh (Inttl Advocare)

Present on behalf of Opponent:

1.Ms. Bitika Sharma,

2. Ms. Nitya Sharma

3.Ms. Vrinda Pathak

Hearing held on 19th May, 2021

Present on behalf of Applicant :

1. Ms. Archana Shanker , registered Patent Agent.
2. Mr. Devinder Singh Rawat , registered Patent Agent
3. Mamta Jha, (Inttl Advocare)
4. Hemant Singh (Inttl Advocare)

Present on behalf of Opponent:

None appeared

Hearing held on 5th August, 2022

Present on behalf of Applicant :

1. Ms. Archana Shanker (Anand and Anand);
2. Hemant Singh (Inttl Advocare)
3. Ms. Mamta Jha (Inttl Advocare);
4. Mr. Devinder Rawat (Anand and Anand);
5. Dr. Sachin Malik (Anand and Anand) and
6. Ms. Garima Mehta (Inttl Advocare)
7. Dr. Atul Bade (Applicant - Novartis)

Present on behalf of Opponent:

1. Ms. Amrita Majumdar
2. Mr. Dominic Alwaris

Hearing held on 7th August, 2022

Present on behalf of Applicant :

1. Ms. Archana Shanker (Anand and Anand);
2. Ms. Mamta Jha (Inttl Advocare);
3. Mr. Devinder Rawat (Anand and Anand);
4. Dr. Sachin Malik (Anand and Anand) and
5. Ms. Garima Mehta (Inttl Advocare)
6. Dr. Atul Bade (Applicant - Novartis)

Present on behalf of Opponent:

Ms. Rajeshwari and others

Hearing held on 3rd November, 2022

Present on behalf of Applicant :

1. Ms. Archana Shanker (Anand and Anand);
2. Ms. Mamta Jha (Inttl Advocare);
3. Mr. Devinder Rawat (Anand and Anand);
4. Dr. Sachin Malik (Anand and Anand) and
5. Ms. Garima Mehta (Inttl Advocare)
6. Dr. Atul Bade (Applicant - Novartis)

Present on behalf of Opponent:

1. Mr. Adarsh Ramanujan,
2. Mr. Skanda Shekhar

ORDER

1. Details and important dates of Application filed by **NOVARTIS AG**. before IPO for grant of the Patent are mentioned herein below:

APPLICATION NUMBER	**4412/DELNP/2007**
APPLICANT NAME	**NOVARTIS AG.**
DATE OF FILING	**08/06/2007**
PCT INTERNATIONAL Application no. & FILING DATE	**PCT/US2006/043710 Dated 08/11/2006**
PRIORITY Application no. &DATE	**US 60/735,093 DATED 09/11/2005**
TITLE OF INVENTION	**"A COMPOUND COMPRISED OF AN ANGIOTENSIN RECEPTOR ANTAGONIST AND A NEP INHIBITOR"**
Date of Request For Examination	**06/11/2009**
PUBLICATION DATE (U/S 11A)	**24/08/2007**
DATE OF FIRST EXAMINATION REPORT (FER)	**30/01/2015**
DATE OF RESPONSE TO FER	**27/11/2015**
HEARING NOTICE U/S 14 ISSUED ON	**06/05/2016**
HEARING U/S 14 HELD ON	**27/05/2016**

Opposition Filed by Indian Pharmaceutical Alliance on	**26/05/2016**
Opposition Filed by NATCO on	**06/09/2016**
Opposition Filed by KUMAR SUSHOBHAN on	**25/08/2017**
Opposition Filed by Dr. Reddy's Laboratories Ltd on	**13/06/2019**
Opposition Filed by Hiren Darji on	**26//02/2020**
Opposition Filed by G. Srinivasa Rao on	**18/09/2020**
Opposition Filed by Dr. Charanjt Kumar Sehgal on	**20/05/2022**
Opposition Filed by KETAKEE S. DURVE **on**	**02/09/2022**
Notice Issued by IPO For Indian Pharmaceutical Alliance	**28/07/2016**
Notice Issued by IPO For NATCO	**05/12/2016**
Notice Issued by IPO For KUMAR SUSHOBHAN	**20/04/2018**
Notice Issued by IPO For Dr. Reddy Laboratories	**07/08/2019**
Notice Issued by IPO For Mr. Hiren Darji	**06/03/2020**
Notice Issued by IPO For G. Srinivasa Rao	**23/10/2020**
Notice Issued by IPO For Dr. Charanjit K. Sehgal	**10/08/2022**
Notice Issued by IPO For Dr. Ketakee Durve	**11/10/2022**

Response filed by Applicant to opposition no 1 **Indian Pharmaceutical Alliance**	**25/10/2016**
Response filed by Applicant to opposition no 2 **NATCO**	**03/03/2017**
Response filed by Applicant to opposition no 3 **KUMAR SUSHOBHAN**	**19/07/2018**
Response filed by Applicant to opposition no 4 Dr. Reddy's Laboratories Ltd.	**06/11/2019**
Response filed by Applicant to opposition no 5 **G.** Mr. Hiren Darji	**06/06/2020**
Response filed by Applicant to opposition no 6 G. Srinivasa Rao	**11/12/2020**
Response filed by Applicant to opposition no 7 **to Dr. Charanjt Kumar Sehgal**	**19/08/2022**
Response filed by Applicant to opposition no 8 KETAKEE S. DURVE	**20/08/2022**
Filing of request for voluntary amendment of claims in respect of Patent Application no. 4412/DELNP/2007 by the applicant, Novartis AG	**06/06/2020**
The applicant filed **Affidavit documents in support of reply statement to Dr. Reddy's Laboratories Ltd:** **(a)** Affidavit of Dr**. Michael Motto with annexure A to** annexure D. **(b)** Affidavit of **Allan S. Myerson** with annexure 1 to annexure 4 **(c)** Affidavit of **Dr. Gauri Billa** on Section 3(d) with annexures	**06/06/2020**
MISCELLANEOUS PETITION ON BEHALF OF THE APPLICANT FOR REJECTING THE INTERVENTION FILED BY NATCO PHARMA LTD	**18/01/2021**

(A) The details of the Eight (8) pre-grant oppositions and their main grounds that heard are as follows:

2. PRE GRANT OPPOSITIONS AND THEIR MAIN GROUNDS OF THE OPPOSITIONS:

I. Indian Pharmaceutical Alliance & Hiren Darji (Opponent 1&5)

i. **Section 25(1) (c):** that the invention so far as claimed in any claim of the complete specification is claimed in a claim of a complete specification published on or after the priority date of the applicant's claim and filed in pursuance of an application for a patent in India, being a claim of which the priority date is earlier than that of the applicant's claim;

ii. **Section 25(1) (d**): that the invention so far as claimed in any claim of the complete specification was publicly known or publicly used in India before the priority date of that claim. Explanation.—For the purposes of this clause, an invention relating to a process for which a patent is claimed shall be deemed to have been publicly known or publicly used in India before the priority date of the claim if a product made by that process had already been imported into India before that date except where such importation has been for the purpose of reasonable trial or experiment only;

iii. **Section 25(1) (e):** that the invention so far as claimed in any claim of the complete specification is obvious and clearly does not involve any inventive step, having regard to the matter published as mentioned in clause (b) or having regard to what was used in India before the priority date of the applicant's claim;

iv. Section 25(1) (f): that the subject of any claim of the complete specification is not an invention within the meaning of this Act, or is not patentable under this Act;

v. Section 25(1) (g): that the complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed;

II. Natco Pharma Ltd. (Opponent 2)**:**

i. Section 25(1) (b) Lack of Novelty
ii. Section 25(1) (e) Lack of Inventive Step
iii. Section 25(1)(f) Subject of Claims 1-7 and 10 is not an invention and is/or are not patentable
iv. Section 25(1)(g) – The complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed
v. Section 25(1)(h) – The applicant has failed to disclose to the Controller the information required under Section 8

iii. G. Sreenivasa Rao spiProPAT Intellectual Property Solutions & Kumar Sushobhan **(**Opponent 3,6)**:**

i. Section 25(1) (b) Lack of Novelty
ii. Section 25(1) (c) Invention has been published before the priority date of the claim
iii. Section 25(1) (e) Lack of Inventive Step
iv. Section 25(1)(f) Subject of Claims 1-10 is not an invention and is/or are not patentable
v. Section 25(1)(g) – The complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed
vi. Section 25(1)(h) – The applicant has failed to disclose to the Controller the information required under Section 8

IV. Reddy's Laboratories Ltd. (Opponent 4)**:**

1. Section 25(1)(e): that the invention so far as claimed in any claim of the complete specification is obvious and does not involve any inventive step, having regard to the matter published as mentioned in clause (b) or having regard to what was used in India before the priority date of the applicant's claim.

2. Section 25(2)(f): that the subject of any claim of the complete specification is not an invention within the meaning of this Act, or is not patentable under this Act

3. Section25(2)(g): that complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed.

V.CHIRAG TANNA INK IDEE (Opponent 7)**:**

I. Section 25 (1) (c)- **KETAKEE S. DURVE**)

II. Section 25(1)(g) — Insufficient disclosure and vague specification

III . Section 25(1)(f)– Not an invention

IV. Section 25 (1) (e) ---- Obviousness/lack of inventive step

VI.KETAKEE S. DURVE (Opponent 8):

a) Section 25(1)(c): Prior claiming

b) Section 25(1)(e): Obviousness/lack of inventive step

c) Section 25(1)(f) – Not an invention / Not patentable

d) Section 25 (1) (h) – Breach of Section 8

Currently pending Claims in the instant Application are as follows:

1. A compound comprising the Angiotensin Receptor Antagonist valsartan and the NEP Inhibitor (2R,4S)-5-biphenyl-4-yl-4-(3- carboxy propionylamino)-2- methyl-pentanoic acid ethyl ester having the formula [((S)-N-valeryl-N-{[2'-(1 H-tetrazole-5-yl)- biphenyl-4-yl]-methyl}-valine) ((2R,4S)-5-biphenyl-4-yl-4-(3- carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester)]Na3 • x H2O, wherein x is 0 to 3.

2. The compound as claimed in claim 1, wherein x is 2.5.

3. The compound as claimed in claim 2, which is trisodium [3-((1S,3R)-1- biphenyl-4-ylmethyl-3-ethoxycarbonyl-1- butylcarbamoyl)propionate-(S)-3'- methyl-2'-(pentanoyl{2''- (tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate.

4. The compound as claimed in claim 1-3, wherein the compound is in crystalline form.

5. The compound as claimed in any one of claims 1 to 4 as and when used in a preparation of pharmaceutical composition or medicament.

6. A method of preparing the compound as claimed in any of claims 1 to 4, said method comprising the steps of: (i) dissolving (S)-N-valeryl-N-{[2'-(1H-tetrazole-5-yl)-biphenyl-4-yl]-methyl}-valine or a salt thereof and (2R,4S)-5-biphenyl-4-yl-4- (3-carboxy-propionylamino)-2-methylpentanoic acid ethyl ester or a salt thereof in a suitable solvent; (ii) dissolving a basic Na compound in a suitable solvent; (iii) combining the solutions obtained in steps (i) and (ii); (iv) precipitation of the solid, and drying same to obtain the dual acting compound; or alternatively obtaining the compound by exchanging the solvent(s) employed in steps (i) and (ii) by (iva) evaporating the resulting solution to dryness; (va) re-dissolving the solid in a suitable solvent; (via) precipitation of the solid and drying same to obtain the compound.

7. The method as claimed in claim 6 wherein the suitable solvent in steps (i) and/or (iva) is acetone.

8. The method as claimed in claims 6 or 7, wherein the basic Na compound is NaOH, Na2CO3, NaHCO3, NaOMe, NaOAc or NaOCHO.

PRE GRANT OPPOSITIONS HEARINGS PROCEDDINGS

The documents relied by the 8 opponents are listed below:

a) **Document 1**: WO2003/059345 (WO '345)/(1538/CHENP/2004)
b) **Document 2**: WO2002006253 (WO '253)
c) **Document 3; US**5217996 (US '996)
d) **Document 4:** EP0443983 (EP '983)
e) **Document 5:** WO2004/078163 (WO '163)
f) **Document 6:** Packer et. al.,
g) **Document 7:** Morissette et. al.,
h) **Document 8:** Almarsson et. al.,
i) **Document 9:** Vishweshwar et. al.,
j) **Document 10:** Etter et. al.,
k) **Document 11:** Aakeroy et. al.,

ARGUMENTS ON MERITS AND HEARING SUBMISSIONS

GROUND I – ANTICIPATION BY PRIOR PUBLICATION / NOVELTY

The opponent 3 & 6 (Kumar sushobhan &G. Srinivasa Rao) submitted that the subject matter of claims of the impugned application which is drawn to a supramolecular complex of valsartan and sacubitril is anticipated by the disclosure of WO'345 i.e. WO 2003/059345. This document discloses a composition comprising valsartan and sacubitril. Valsartan is described in the document as AT1-Antagonist and Sacubitril is described as NEP inhibitor (page 82). As per WO345, the compounds in the composition may be present in the form of pharmaceutically acceptable salt. The relevant portion is extracted herein below for ready reference:

*"... **The compounds to be combined can be present as pharmaceutically acceptable salts.** If these compounds have, for example, at least one basic center, they can form acid addition salts. Corresponding acid addition salts can also be formed having, if desired, an additionally present basic center. **The compounds having at least one acid group (for example COOH) can also form salts with bases.** Corresponding internal salts may furthermore be formed, if a compound comprises e.g. both a carboxy and an amino group..."*

The opponent no 3 & 6 submitted that **WO345** also states that the pharmaceutical salt of the APIs of the composition may be in hydrate form "*The **corresponding active ingredient or a pharmaceutically acceptable salt thereof may also be used in form of a hydrate***". WO345 claims a composition comprising valsartan and sacubitril.

The opponent no 3 & 6 submitted that the following admissions of the Applicant establish that the supramolecular compound of valsartan and sacubitril fall within the scope and ambit of WO'345:

The opponent no 3 & 6 submitted that it is well recognized that a supramolecular compound is nothing but a polymorphic form – re- US FDA guidelines. Such being the accepted position in the art, it is incumbent on the Applicant to demonstrate how the supramolecular compound has any therapeutic efficacy better than the closest prior art. As discussed in preceding paragraphs under the heading of inventive step, the cited closest prior art WO'345 already teaches combination of valsartan or pharmaceutically acceptable salt thereof and N-(3-Carboxy-1-oxopropyl)-(4s)-p- phenyl phenyl methyl)-4-amino-2R-methyl butanoic acidethyl ester [a NEP inhibitor (Sacubitril)] together in a composition. WO'345 discloses on page 7 that: *"It has surprisingly been found that, a combination of valsartan and a NEP inhibitor achieves greater therapeutic effect than the administration of valsartan, ACE inhibitors or NEP inhibitors alone and promotes less angioedema than is seen with the administration of a vasopeptidase inhibitor alone. Greater efficacy can also be documented as a prolonged duration of action"*. It is further disclosed on page 7 of WO'345 that lower doses of the individual drugs to be combined according to the present invention can be used to reduce the dosage, for example, that the dosages need not only often be smaller but are also applied less frequently, or can be used to diminish the incidence of side effects.

The combined administration of valsartan or a pharmaceutically acceptable salt thereof and a NEP inhibitor or a pharmaceutically acceptable salt thereof in the supramolecular compound/complex, as per the Applicant, results in a significant response in a greater percentage of treated patients.

The Applicant however, has failed to provide any comparative data establishing the enhanced therapeutic efficacy of the supramolecular compound over what is already known in the prior art WO'345 in the as filed application of In4412. In absence of lack of enhanced therapeutic efficacy the subject matter of impugned application is not patentable under Section 3(d).

THE PATENT APPLICATION IN 4412-no therapeutic efficacy established:

The opponent no 3 & 6 (Kumar sushobhan &G. Srinivasa Rao) submitted the patent application IN 4412/DELNP/2007 attempts to demonstrate the efficacy of the combination of valsartan and sacubitril as a supramolecular complex (pages 34-35 - internal page of application). As would be evident from page 35, for assessing the in vivo antihypertensive effect of the supramolecular complex, the complex is compared with vehicle i.e. one group of animals are administered, the supramolecular complex and another group is administered vehicle i.e. water or alcohol. The same applies to the experiments done to assess inhibition of NEP in vivo. No actual values are declared.

However, a conclusion is arrived; "*the available results indicate an unexpected therapeutic effect of the compound according to the invention*".

The opponent no 3 & 6 (Kumar sushobhan &G. Srinivasa Rao) submitted that the dosage of the complex is similar to the dosage of the valsartan-sacubitril composition of WO'345.

WO'345	**IN 4412/DELNP/2007**
Valsartan is supplied in the form of suitable dosage unit form, for example, a capsule or tablet, and comprising a therapeutically effective amount, e.g. from about 20 to about 320 mg. of valsartan which may be applied to patients. In case of NEP inhibitors, preferred dosage unit forms are, for example, tablets or capsules comprising e.g. from about 20 mg to about 800 mg, preferably from about 50 mg to about 700 mg, even more preferably from about 100 mg to about 600 mg and even	The ARB component is administered in a dosage of from about 40 mg/day to about 320 mg/day and the NEPi component is administered in a dosage of from about 40 mg/day to about 320 mg/day. More specifically, the dosage of ARB/NEPi, respectively, include 40 mg/40 mg, 80 mg/80mg, 160 mg./160mg, 320 mg/320 mg, 40 mg/80 mg, 80 mg/160 mg, 160 mg/320 mg, 320 mg/640 mg, 80 mg/40 mg, 160 mg/80 mg and 320 mg/160 mg, respectively. These dosages are therapeutically effective amounts.

The opponent no 3 & 6 (Kumar sushobhan &G. Srinivasa Rao) submitted on :REPLY STATEMENT FILED BY APPLICANT

As per the Reply Statement (para 38), the unexpected and surprising effect of the supramolecular compound is that it is less hygroscopic as compared to valsartan or sacubitril taken

individually. The Applicant very carefully avoids to state what the therapeutic efficacy of the compound is

The opponent no 3 & 6 (Kumar sushobhan &G. Srinivasa Rao) submitted on DOCUMENTS/EVIDENCE FILED ON 6.6.2020:

Affidavit of Dr Motto:

Para 18- the advantage, as per Dr Motto of preparing the supramolecular compound is that it provides the effect of both valsartan and saccubitril in a single compound;

Para 19- *it was not known what would be the optimal amount of valsartan and saccubitril to be administered to a patient*- Please see WO'345 pg 15 (internal)- valsartan dose – 160 to 320 mg per day; saccubitril – 100-300mg per day;

Para 20- the compound LCZ696 has superior crystallinity, low hygroscopicity, stability, solubility and bioavailability as compared to the active ingredients;

Para 22- greater solubility – hence lower dose can be used - same conclusion as pg 7 of WO'345 "***Further benefits are that lower doses of the individual APIs to be combined according to the present invention can be used to reduce the dosage, for example, that the dosages need not only often be smaller but are also applied less frequently, or can be used to diminish the incidence of side effects***."

Para 24: Increased solubility has an impact on bioavailability – the supramolecular compound is more bioavailable than valsartan.

Affidavit of Dr. Billa: Dr. Billa elaborates on the clinical trial evidence and the nature of Vymada as a breakthrough drug. She neither compares the efficacy produced by Vyamada with Valsartan and Sacubitril administered together nor does she state in any manner that the therapeutic efficacy of the Vymada is better than therapy with Valsartan and Sacubitril administered together.

Jessie Gu et al (pg 47 of documents dated 6.6.2020)

The opponent no 3 & 6 (Kumar sushobhan &G. Srinivasa Rao) submitted: This is a study based on comparison of LCZ696 with valsartan alone – this is evident from the "Study Design" – pg 49 "a dose escalation study examined the single and multiple dose pharmacokinetics and pharmacodynamics of ascending oral dose of LCZ696 and a bioequivalence study to evaluate the relative exposure of valsartan following administration of LCZ696 or valsartan". Thus, LCZ696 was compared to valsartan alone.

The conclusion arrived at (pg 58) was *"the bioavailability study demonstrated that systemic exposure to valsartan following a single 400mg dose of LCZ696 was equivalent to that following administration of 320mg of valsartan, a dose that has proven anti-hypertensive efficacy. .."*

In response to the Opponent's argument that the claimed supramolecular complex has no therapeutic efficacy, the Applicant attempted to show through the papers of Izzo et al, the

affidavits and other papers that the complex/compound has better bioavailability as compared to the free compounds Valsartan and Sacubitril.

The opponent no 3 & 6 (Kumar sushobhan &G. Srinivasa Rao) submitted*:* This argument is also liable to be rejected because:

a) As per the law laid down in the case of Novartis V Union of India- a showing of better bioavailability is not sufficient to demonstrate therapeutic efficacy;

b) Clearly, there is no evidence whatsoever to demonstrate that the therapeutic efficacy' i.e the lowering of blood pressure achieved by the use of the supramolecular complex;

c) The papers and the affidavits do not make out the case that the supramolecular complex is a new chemical entity –therefore, the bar under sec 3(d) would be applicable and has not been crossed by the Applicant;

'Therapeutic efficacy' in medical terms is the ability of a product or treatment to provide a beneficial effect {ref: https://www.news-medical.net/health/What- Does-Efficacy-Mean.aspx]. The Supreme Court in Novartis V Union of India clarified that *efficacy must be seen in the desired or intended use of the product of the invention, and that in the case of medicines, whose function is to cure disease, the test of efficacy can be only "therapeutic efficacy"*.

The opponent no 3 & 6 (Kumar sushobhan &G. Srinivasa Rao) submitted: On the other hand, bioavailability is merely the amount of drug that is able to enter the circulation inside a body in order to achieve a certain active effect. Whether after entering the body, the substance does produce 'any better curative effect' is something that has to be shown through experimentation. In the present case, no such evidence is placed on record.

What the Applicant has placed on record is that the drug is absorbed into the body (greater bioavailability). However, its effect after reaching blood stream is left open and would depend on many factors such as action of liver enzymes, plasma proteins, chemokines, etc that act on drug. Furthermore, even after reaching target site, whether the supramolecular complex has penetrated inside the organ and achieved better therapeutic effect is something the Applicant has failed to demonstrated through research.

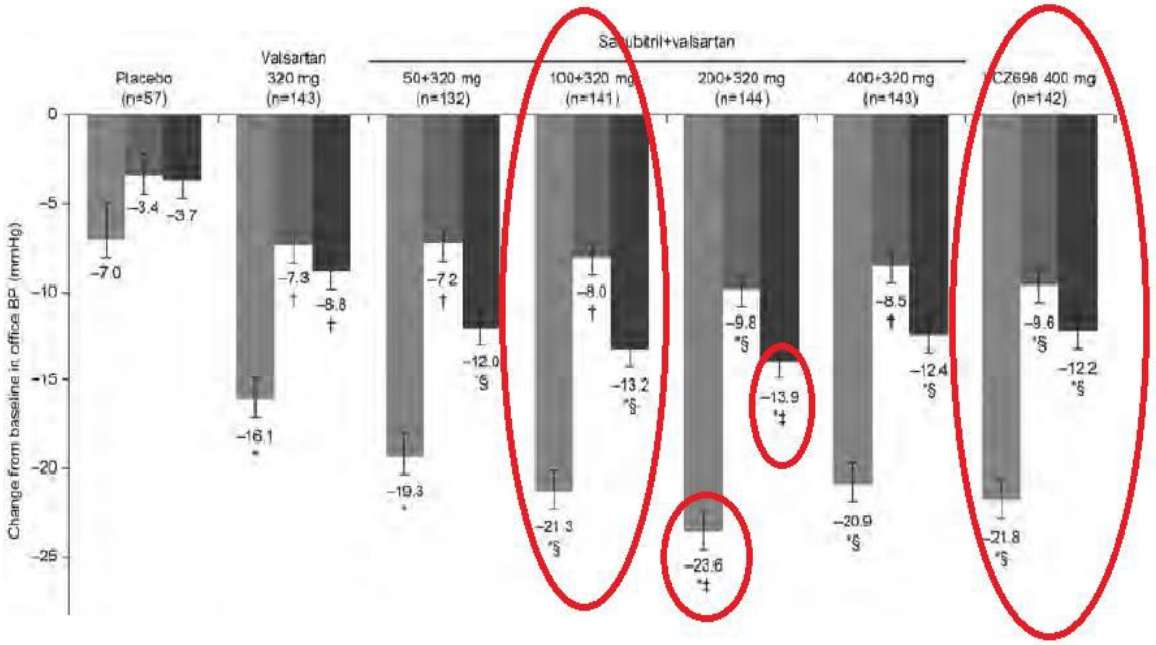
Paper relied on by Applicant	Conclusion
Izzo et al	Shows that 400mg of supramolecular complex is able to produce the same/similar effect as 320mg of Valsartan and 200mg of Sacubitril. – no increase or reduction in blood pressure lowering shown
Murray et al	Therapy with combination of Angiotensin receptor blocker with NEP inhibitor is better than therapy with combination of ACE inhibitor with NEP inhibitor.
Jessie Gu et al	Therapy with combination of Valsartan with Sacubitril needs lesser amount of Valsartan as compared to when Valsartan is given alone.

clearly, there is no data regarding therapeutic efficacy of the supramolecular complex is placed on record.

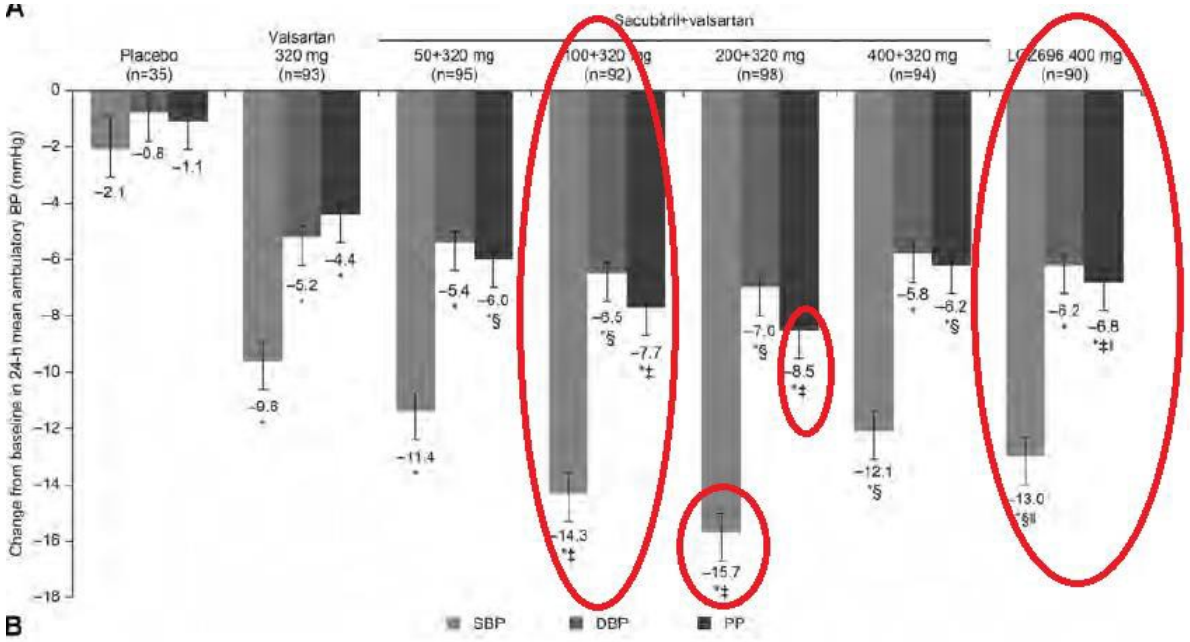
The opponent no 3 & 6 (Kumar sushobhan &G. Srinivasa Rao) submitted that Izzo et al published in 2017: The paper attempts to compare the safety and efficacy of crystalline valsartan/sacubitril with placebo and combination of free valsartan and sacubitril. As a result of the study, as evident from the extract, the effects are similar in both cases.

As per the abstract "*The SBP reduction with LCZ696 400 daily were similar to the co-administered free valsartan 320 mg and sacubitril 200 mg. Effects were similar in those older and younger than 65 years and active therapies had adverse event rate similar placebo, we conclude that crystalline valsartan and sacubitril 400 mg daily (1)is superior to valsartan 320 mg for lowering SBP; (2) has similar efficacy to the combination of free valsartan 320 mg + free sacubitril 200 mg; (3) represents the optimal dosage for systolic hypertension in patients of any age and (4) is safe and well tolerated*".

A close examination of the paper reveals that the efficacy in lowering blood pressure level as shown in figure 2A in respect of the supramolecular complex LCZ696 400 mg is in fact inferior to free valsartan and sacubitril administered. Said Fig 2A is reproduced below for ready reference and the values of reduction in BP obtained by LCZ696 and Sacubitril 100mg + Valsartan 320mg is encircled.



The opponent no 3 & 6 (Kumar sushobhan &G. Srinivasa Rao) submitted : Review of the Fig 2B also reveals that the efficacy in lowering blood pressure level as shown in figure 2A in respect of the supramolecular complex LCZ696 400 mg is in fact inferior to free valsartan and sacubitril administered. Said Fig 2B is reproduced below for ready reference and the values of reduction in BP obtained by LCZ696 and Sacubitril 100mg + Valsartan 320mg is encircled.



The opponent (Kumar Sushobhan & G. Sriniwas Rao) no 3 & 6 submitted:

Further, an analysis of the quantified data presented Figure 2A and 2B Izzo et al reveals that the effect produced by 400mg of supramolecular complex (LCZ696) is lesser than the effect produced by 320mg Valsartan with 200mg Sacubitril. The effect measured as decrease in Hypertension is reflected in minus values and is summarized in the table below for ready reference of the Ld Controller:

Data for decrease in BP as per Figure 2A

	SBP	*DBP*	*PP*
320mg Valsartan with**200mg Sacubitril**	-23.6	-9.8	-13.9
400mg LCZ696 (the supramolecular complex) contains **204mg Valsartan and 198mg Sacubitril**	-21.8	-9.6	-12.2

Data for decrease in BP as per Figure 2B

	SBP	*DBP*	*PP*
320mg Valsartan with**200mg Sacubitril**	-15.7	-7.0	-8.5
400mg LCZ696 (the supramolecular complex)**204mg Valsartan and 198mg Sacubitril**	-13.0	-6.2	-6.8

SBP stands for Systolic Blood Pressure DBP stands for Diastolic Blood Pressure PP stands for Pulse Pressure

The opponent (Kumar Sushobhan & G. Sriniwas Rao) no 3 & 6 submitted:

What is even more striking from the quantified data given in Izzo et al is that 320mg Valsartan with 100mg Sacubitril is able to produce similar effect than 400mg LCZ696 (the supramolecular complex). The data for reduction in Hypertension disclosed in Figure 2A and 2B for 320mg Valsartan with 100mg Sacubitril and 400mg LCZ696 is summarized in table below for the ready reference of Ld Controller:

Data for decrease in BP as per Figure 2A

	SBP	*DBP*	*PP*
320mg Valsartan with**100mg Sacubitril**	-21.3	-8.0	-13.2
400mg LCZ696 (the supramolecular complex) contains **204mg Valsartan and 198mg Sacubitril**	-21.8	-9.6	-12.2

Data for decrease in BP as per Figure 2B

	SBP	*DBP*	*PP*
320mg Valsartan with**100mg Sacubitril**	-14.3	-6.5	-7.7
400mg LCZ696 (the supramolecular complex)**204mg Valsartan and 198mg Sacubitril**	-13.0	-6.2	-6.8

SBP stands for Systolic Blood Pressure DBP stands for Diastolic Blood Pressure PP stands for Pulse Pressure

The opponent 3 &6 (Kumar Sushobhan & G. Sriniwas Rao) submitted that therefore, the paper of Izzo which is a publication by Novartis states that the effect produced by 400mg supramolecular complex is "similar" to the effect produced by 320mgValsartan with 200mg Sacubitril. However, an analysis of the quantified data disclosed in said document reveals that the effect produced by 400mg supramolecular complex is **not similar** rather it is **lesser than** the effect produced by 320mgValsartan with 200mg Sacubitril. Further, the analysis of the quantified data disclosed in said document also reveals that the effect produced by 400mg supramolecular complex is **similar** to the effect produced by 320mgValsartan with 100mg Sacubitril even though the supramolecular complex contains double the amount of Sacubitril i.e. 198mg. This data establishes that LCZ696 is actually inferior to physical mixture of valsartan and sacubitril since almost double the dose of sacubitril is required in LCZ696 to produce similar effect as physical mixture of Valsartan 320mg and Sacubitril 100mg.

The opponent (Kumar Sushobhan & G. Sriniwas Rao) no 3 & 6 submitted:

The Applicant argued that there is a dose reduction of Valsartan in supramolecular complex since the supramolecular complex contains 204mg Valsartan and the marketed dose of Valsartan being given to patients in Izzo is 320mg.

However, WO253 explicitly teaches that the hydrate salt form of Valsartan such as disodium Valsartan hemihydrate has better solubility and bioavailability than the free acid Valsartan. Since it was known in art that salt hydrate form of Valsartan has higher bioavailability as compared to free acid form of Valsartan, it is implied that for achieving similar level of bioavailability, the required amount of salt hydrate form of Valsartan will be lesser than the required amount of free acid form of Valsartan.Therefore, the change in dose level of Valsartan stated by Izzo et al is nothing but mere re-affirmation of knowledge which was already commonly known in art by

way of publications such as WO2002/06253. Further, the publication of Murray relied on by Applicant is a comparison of the supramolecular complex with a drug of another category i.e. Enalaprilat which was commonly used for treating Hypertension at the time of the invention. **US996** discloses the dose of Sacubitril to be given to a 70kg mammal for effective treatment of hypertension (a mammal includes a human being and 70 kg is understood in medical field to the average weight of an adult human male). Further, US996 also states that *"The dosage of active compound is dependent on the species of warm-blooded animal (mammal), the body weight, age and individual condition, and on the form of administration."* This statement as well as the dose disclosed in US996 establishes the therapeutic efficacy of Sacubitril in treatment of hypertension.[Please refer lines 59 to 64 in column 18 of US996 WO345 discloses that Valsartan and Sacubitril should be used together.

WO345 also discloses the doses of Valsartan and Sacubitril to be used when the two drugs are combined together.

In light of the disclosure of WO345, US996, and WO253 following facts were established in the field at the time of the invention:

a. The therapeutic effect of Valsartan as well as Sacubitril in treatment of hypertension and related diseases was known.
b. The dose of Valsartan and Sacubitril to be given to a patient when these drugs were being used individually as monotherapy was known.
c. It was established that when Valsartan and Sacubitril are given together to a patient, the dose of the drugs gets reduced and there is better efficacy with lesser side effects as compared to monotherapy with either Valsartan or Sacubitril.

Thus, in view of the above, for a PSITA Valsartan with Sacubitril is a "substance" which was known to have enhanced therapeutic efficacy as compared to valsartan alone or sacubitril alone.

The dose in this "substance" Valsartan with Sacubitril should be given to a patient was known. The pharmacological effect produced by this "substance" at particular doses was known and quantified.

Since, Valsartan with Sacubitril is a known substance with known efficacy, the claimed subject matter of impugned application attracts Section 3(d) and it is incumbent upon the Applicant to prove enhancement in therapeutic efficacy achieved by the complex which is the subject matter of impugned application as compared to the therapeutic efficacy of Valsartan with Sacubitril.

- In the specification, there is no demonstration of enhanced therapeutic efficacy;
- In the reply statement, the only efficacy alluded to is "less hygroscopicity" as compared to valsartan- there is nothing about bioavailability or solubility;

- The evidence of Dr Motto- fails to demonstrate greater efficacy; it only states that the valsartan in Entresto is more bioavailable than marketed formulation of valsartan- there is no attempt to demonstrate any therapeutic efficacy;

- Dr. Billa attempts no comparison of the therapeutic efficacy exhibited by LCZ696 with a therapy when Valsartan and Sacubitril administered together.

- Gu et al- the supramolecular compound/complex was compared to Valsartan and found to have similar antihypertensive effect;

- Izzo et al published in 2017: this paper states that the supramolecular compound/complex *has similar efficacy to the combination of free valsartan 320 mg + free sacubitril 200 mg.* Whereas, the data reveals that LCZ696 is actually inferior to physical mixture of Valsartan Sacubitril, as explained above.

Thus, there is no direct comparison of composition of WO'345 with the supramolecular complex in the specification of IN4412. There is no data or any material to demonstrate the that therapeutic efficacy of the supramolecular complex greater than the composition of WO'345- rather it shows they have comparative effect at best.

Thus, the Applicant has failed to demonstrate any therapeutic efficacy as required under Section 3(d). On this ground alone, the application is liable to be rejected.

Applicants (NOVARTIS AG.) Arguments and Submission on PRIOR PUBLICATION / NOVELTY

The applicant argued that one of the main distinguishing feature of the present invention with respect to WO'345 is that the present invention is directed to a single dual acting compound whereas WO '345 is directed to a composition comprising a combination of (a) AT-1 antagonist valsartan or a salt thereof, and (b) a NEP inhibitor, in particular (2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2- methyl-pentanoic acid ethyl ester or a salt thereof.

The applicant further submitted that from page 13 of WO '345 where it is clearly stated that "two components can be administered together, one after the other or separately in one combined unit dose form or in two separate unit dose forms (separate containers)."
The agent for applicant argued that there is no reference whatsoever to a single dual-acting compound (unique novel compound) that combines two active ingredients by two different mode of action having an intricate network and stabilized by an involved network of ionic,
hydrogen and coordination bonds, which has been described in various ways in
the IN'4412 specification.

The agent for applicant further submitted that the process of WO 345 does not result in a compound of present invention. The process disclosed in the present invention provides a unique synthesizing route resulting in a unique compound

The applicant argued that In particular, in WO'345 :

a) There is no reference to supramolecular compounds, complexes or cocrystals in WO'345.

b) **Single Compound:** in the present invention valsartan and sacubitril are constituents of a single defined compound, whereas in WO'345 the chemical relationship between the individual active substances valsartan and sacubitril is left open..

c) **molar ratio is 1:1:** in the invention, valsartan and sacubitril are provided in the particular molar ratio of 1:1, whereas the ratios of valsartan and NEP inhibitor which may be administered are left open in WO'345 (see, for instance, WO'345, page 15, 2nd para).

The applicant argued that, **"the claimed invention is novel".**

ANTICIPATION BY PRIOR CLAIMING

The Opponent no 8 (KETAKEE S. DURVE) submitted that D1 is the Indian application of the same patent applicant, i.e., Novartis, with the earliest priority date of 17.01.2002. D1A is the corresponding PCT application of D1 having the same priority date. In contrast, the subject application has a later priority date of 09.11.2005. D1 is undoubtedly a specification filed in pursuance of an application in India.

D1A, in principle, is also a specification filed in pursuance of an application in India in view of S. 7(1A) read with S. 138(4)—an international application designating India is deemed to be an application under this Act since the corresponding application (D1) has been filed in India.

. Therefore, the only remaining question is whether the claims of the subject application are already claimed in D1 and/or D1A. The opponent has two submissions in this respect:

The Opponent no 8 (KETAKEE S. DURVE) argued that the patent applicant has admitted that D1 (which came to be granted as Indian Patent No. 229051) claims the alleged supramolecular complex of valsartan and sacubitril with sodium atoms and water molecules. **This admission is recorded in a judgment dated 28.10.2021 in the case of *Novartis AG* v. *NATCO Pharma Ltd.* [C.S. (Comm.) 62/2019].** A copy of this order was handed over during the hearing but is enclosed with the present written submissions for completeness of record. The prior claim of D1 and/or D1A is a document addressed to the person skilled in the art and, thus, cannot have inconsistent claim constructions at different points in time. It is for this reason that patent law recognises that a patent applicant cannot take inconsistent stands on claim construction of the very same patent to obtain different benefits at different points in time. [See Interactive Gift Express, Inc. v. Compuserve Inc., 256 F.3d 1323 (Fed. Cir.2001)] A copy of this judgment was handed over during the hearing but is enclosed with the present written submissions for completeness of record.

The Opponent (KETAKEE S. DURVE) 8 further submitted that the same patent applicant, Novartis, obtained the benefit of an interim injunction before an Indian court in Novartis AG v. NATCO Pharma Ltd. (supra), stating that by claim construction of D1/D1A, the supramolecular complex of valsartan and sacubitril with sodium atoms and water molecules is claimed in claim 1 of D1 [paras 8, 9, 16, 28, 39, 40, 52, 57 & 58 of the Novartis AG v. NATCO Pharma Ltd.

order dated 28.10.2021 (supra)]. Therefore, the patent applicant cannot contend the opposite today in this proceeding. Automatically, therefore, a case under S. 25(1)(c) is made out since the very same subject matter is claimed in the prior claim.

The Opponent (KETAKEE S. DURVE) 8 argued that above, a case of double patenting and/or prior claiming is made out even on 1st principles. Claim 1 of D1 and/or D1A expressly refer(s) to both valsartan and sacubitril. This is not disputed fact. Said claim 1 of D1 and/or D1A uses the connecting phrase 'comprising'. It is now too well settled in patent law that the transition phrase "comprising" is an open-ended connector, i.e., that the patent claim will cover anything that includes the mentioned components, even if there are additional elements. Consequently, a claim for a product 'comprising' valsartan and sacubitril will necessarily include any product with both of these and other components, such as sodium atoms or water molecules. Any complex comprising valsartan and sacubitril would automatically get covered within the scope of the claim because of the use of the openended connector 'comprising'.

The Opponent no 8 relies on the order of the Hon'ble Delhi High Court, *vide* judgment dated 02.11.2020 in *Astrazeneca AB & Anr.* v. *Intas Pharmaceutical Ltd.* [C.S. (Comm.) 410/2020; @ para 22.8] has affirmed the following test:

The Court went on to re-write the claim to make plain this differentiation. The patentees contended [an aspect which was noticed by the Court] that such notional dismemberment of their claim

necessarily involved destruction of the generality of the inventive step and, thus, deprived them of the real differentiation between what they sought to protect and that which was cited as prior document. The Court, in this background, made the following pertinent observations.

"...
There would appear to be no ground for construing the phrase "the invention so far as claimed in any claim" in different senses in the sub-divisions of section 14(1), so that, if the cited prior claim on its fair construction can be seen to grant as a manner of manufacture that which the later claim on its fair construction would remonopolise, the objection of prior claiming is established, and this despite the inclusion in the later claim of variants of the manner of manufacture to which no objection can properly be raised. The later circumstance will of course be of concern in the determination of the relief to be accorded if and when the plea is established, but it cannot shield a vulnerable embodiment of the invention claimed from attack on the ground of preclaiming any more effectively than it can from the other objections available at the opposition stage."

The opponent no 8 submitted that this judgment was appelaed to the Division Bench, which upheld the same and the Supreme Court dismissed the SLP against it. A copy of the afore-quoted judgment has already been enclosed with the present written submissions.

The opponent (KETAKEE S. DURVE) argued that On fact, there is no denial that even a supramolecular complex is within the monopoly of the earlier patent. A separate claim is not required for prior claiming purposes. Therefore, a supramolecular complex of sacubitril and valsartan sodium atoms or water molecules remains claimed in claim 1 of D1 and/or D1A. Therefore, a case under S. 25(1)(c) is made out.

The agent for applicant submitted that the Opponent's argument on prior claiming that the Valsartan and Sacubitril supramolecular complex of the IN '4412 application has been already claimed in the earlier patent, (D1: 1538/CHENP/2004 / IN229051), is flawed. The Opponent at the hearing relied on the doctrine of judicial estoppel, i.e., one cannot take inconsistent position in different proceeding. In this regard, the Opponent has relied on the following cases.

a) *Interactive Gift Express, Inc. Vs. Compuserve Incorporated* and Anr, United States Court of Appeals, Federal Circuit. (Jul 13, 2001); 256 F.3d 1323; 2001 WL792669 (*Annexure 9 filed by the Opponent*).

b) *Novartis AG & Ors vs Natco & Ors*, DHC order of Hon'ble Mr. Justice Jayant Nath, dated 28-Oct-2021 in C.S. (Comm) 62/2019 & Ors (*Annexure 10 filed by the Opponent*).

c) *AstraZeneca AB & Ors vs. Intas Pharmaceuticals & Ors in C.S. (Comm) 410/2020* by Hon'ble Justice Rajiv Shakdher *Annexure 11 filed by the Opponent*.

The applicant further submitted that prior claiming under the provisions of the Indian Patents Act is contained in Section 13(1)(b). The purpose of prior claiming is to ensure that one invention should be granted one patent (Section 46(2) of the Indian Patents Act).

The applicant submitted that the several provisions of the Indian Patents Act according to which in case of prior claiming, the Learned Controller can under Rule 31 may direct the Applicant to

make a reference of the earlier filed patent application in the subsequently filed application. This is also in view of Section 18(2) of the Indian Patents Act.
The applicant further submitted that a commercial product can be covered by more than one patent. An infringer can infringe more than one patent for one commercial product.

The applicant pointed out Rule 32 and Section 19(1) of the Indian Patent Rules that states as follows:
Rule 32 *If in consequence of an investigation made under section 13, it appears to the Controller that the applicant's invention cannot be performed without substantial risk of infringement of a claim of another patent, the applicant shall be so informed and the procedure provided in rule 29 shall, so far as may be necessary, be applicable.*

Section 19(1) *19. Powers of Controller in case of potential infringement-*

(1) If, in consequence of the investigations required [under this Act], it appears to the Controller that an invention in respect of which an application for a patent has been made cannot be performed without substantial risk of infringement of a claim of any other patent, he may direct that a reference to that other patent shall be inserted in the applicant's complete specification by way of notice to the public, unless within such time as may be prescribed-

(a) the applicant shows to the satisfaction of the Controller that there are reasonable grounds for contesting the validity of the said claim of the other patent; or

(b) the complete specification is amended to the satisfaction of the Controller.

The applicant submitted that even the working statements contemplate that one commercial product can be covered by more than one invention. To demonstrate prior claiming u/s 25(1)(c) of the Indian Patent Act, Opponent must show that

"*the invention so far as claimed in any claim of the complete specification is claimed in a claim of a complete specification published on or after priority date of the applicant's claim and filed in pursuance of an application for a patent in India, being a claim of which the priority date is earlier than that of the applicant's claim*".
Thus, only the claims of the cited specification may be looked on for assessing prior claiming.

The applicant submitted Further, to demonstrate prior claiming, the subject matter of the challenged invention must have been claimed in an ***individualized claim*** of the cited specification, as set forth in the decision of ***Daikin Kogyo Co. Ltd. (Shurgu s) Application, [1974] RPC 559 (****Annexure 12****)***

"Where an earlier claim is wider in its scope than a later claim and there is no separate claim in the earlier specification restricted to the subject-matter of the later claim, the claimant of the earlier claim cannot, in my judgment, assert that he has made a prior claim to the subject matter of the later claim."

The applicant argued that, the legal and technical arguments made by the Opponent by relying on the concept of judicial estoppel as provided in *Interactive Gift Express, INC. VS. Compuserve Incorporated* case of the US Court of Appeals is misplaced and incorrect.

The applicant submitted the Opponent in order to invoke judicial estoppel relied on the decision of the ***Hon'ble Justice Jayant Nath in C.S. (Comm) 62/2019 (hereinafter referred to as 62/2019) dated October 28, 2021***. The Opponent is incorrectly reading the said decision and concept of judicial estoppel. The Patent Applicant/ Petitioner (in 62/2019) has not made any inconsistent pleadings and Opponent has misplaced and misconceived Patent Applicant's averments before the Court.

The applicant argued that the Opponent has attempted to misguide the Ld. Controller. It is submitted that patentability and infringement are two different concepts and issues. Infringement is an issue of violation of Patentee's rights conferred under section 48, whereas patentability is an issue involving novelty, inventive step and technical advancement under section 2(1)(j), 2(1) (ja), section 3, section 10 and section 13 of the Patents Act. Subsequent technical advancement, if it embodies or encompasses features of earlier patented invention, would infringe such earlier patent. Likewise, the fact that subsequent technical advancement infringes an earlier patent is not a ground for refusal of grant of patent nor is it a ground for opposition or revocation of a patent under section 25 and 64 of the Patents Act. This is also evident from reading of section 19 of the Patents Act, 1970. Reference may be made to: *Hindustan Lever vs. Lalit Wadhwa*, 2007 (35) PTC 377 (Del) (paras 14-16), enclosed as *Annexure 13*.

The applicant submitted that C.S (Comm) 62/2019 is in relation to suit for infringement filed by the Applicant for infringement of Indian Patent No. 229051 (equivalent of D1/D1A). It is submitted that there is no statement made by the Applicant in the said proceedings before the High Court or are there any findings made by the Hon'ble Judge in 62/2019 that support judicial estoppel and that the supramolecular compound of the present invention i.e IN 4412 is disclosed in D1/D1A.The Opponents contention is flawed for the following reasons:

(i) The Interactive decision relied upon by the Opponent for judicial estoppel is a US Federal Court Decision. The proceedings in the said case in US were in relation to a proceeding relating to the **same patent** before the **trial court as well as the Appeal Court**. Therefore, the subject matter before the trial Court and the Appeal Court was in relation to the same invention. Clearly the said decision at page 23 held that the Doctrine of Judicial estoppel is to prevent a party from adopting inconsistent legal provisions in the sameorrelated judicial proceedings and that a party will be judicially estopped from asserting a position on appeal that is inconsistent with the position it advocated before the trial court.

The applicant submitted that in C.S (Comm) 62/2019 all statements were made by the Applicant with regard to infringement of a patent for a combination comprising Valsartan and Sacubitril and the Courts carried out claim construction for the purpose of infringement.

The Opponent relies on para 28 of the said order of Hon'ble Justice Jayant Nath in CS (Comm) 62/2019 to demonstrate that while asserting IN 229051, the invention comprises combination of Valsartan and Sacubitril without any limitation in terms of salts, crystalline form, amorphous form, polymorphic forms, hydrates, supra molecular structure (supra-molecular complex), or mixture thereof.

The applicant submitted that the said case before the High Court was about infringement of a commercial product of NATCO that infringes IN 229051 as well as IN4412 as and when granted. The infringing product of NATCO contained all the integers of the granted claim of the suit patent IN'229051 and it fell within/was encompassed by the claim coverage and thus amounted to infringement.

The applicant submitted that (iv) **The Applicant submits that IN 229051 is basic patent where the Applicant for the first time claimed an invention for a combination of Valsartan or a pharmaceutically acceptable salt and Sacubitril or a pharmaceutically acceptable salt**.

In para 30 of the said order, the Plaintiff's (the Applicant herein) statement has clearly been recorded as follows:

"Learned counsel for the plaintiffs has however clarified that on a plain reading of Claim I what is protected is a combination of Valsartan or a pharmaceutically acceptable salt and Sacubitril or a pharmaceutically acceptable salt and a pharmaceutically acceptable carrier. If the defendant were to only sell a combination of Valsartan and Sacubitril as a supra molecular complex without adding pharmaceutically acceptable carrier, it would not be covered by Claim I of the suit patent"

In para 9 of the said order, it is recorded that the Plaintiff's (the Applicant herein) have clearly stated the following:

"*It is further urged that after filing of the patent application, plaintiff No. 1 continued with additional experimentation. After much research, plaintiff No. 1 arrived at a supra molecular structure (or supra molecular complex) of Valsartan and Sacubitril. It is urged that the said supra molecular structure is a novel compound wherein two anionic components of Valsartan and Sacubitril together with sodium cations and water molecules are linked together non-covalently to form a single large and highly intricate supra molecular structure. It is stated that being a novel supra molecular structure, plaintiff No. 1 has filed an application for grant of patent in respect thereof and the same is subject matter of Indian Patent application No. 4412/DELNP/2007 dated 08.11.2006. The said application was published on 24.08.2007. It is stated that the said application has been opposed by way of pre-grant oppositions by various parties including the defendant herein. The opposition by the defendant was filed on 06.09.2016 though the patent application was published in 2007 and is pending adjudication*."

The applicant argued that hence, mere fact that a patent has been granted for D1 is irrelevant to the issue of patentability of the subject patent for a dual acting compound/supramolecular complex

The applicant submitted that the Opponent relied on the AstraZeneca order of Hon'ble Justice Shakdher on the issue of prior claiming. In fact, the paragraphs relied upon by the Opponent do

not deal with the issue or prior claiming. Having said this, it was a duty of the Opponent to direct the Learned Controller's attention to at least two decisions of the Delhi High Court of Hon'ble Justice Hari Shanker that specifically deal with the issue of prior claiming and also deal with the decision of Justice Shakdher. Both the decisions of Hon'ble Justice Hari Shanker are post the decision of Hon'ble Justice Shakdher in the AstraZeneca decision. The two decisions of Hon'ble Justice Hari Shanker are:

(a) FMC Corp & Anr Vs. Best Crop Sciences in IA 2084/2021 in C.S. (Comm) 69/2021 dated July 7, 2021 (*Annexure 14*) and

(b) Novartis vs. Natco in C.S. (Comm) 256/2021 of December 13, 2021 (*Annexure 15*).

FMC Corp & Anr Vs. Best Crop Sciences, C.S. (Comm) 69/2021 dated July 7, 2021

The relevant sections of the FMC order that deal with the issue or prior claiming wherein the Hon'ble Judge has distinguished the AstraZeneca Order is para 12.1 to 12.21 from pages 111-124. The Court came to the conclusion that in order to succeed on the ground of prior claiming, a claim-to-claim comparison is necessary. The Hon'ble Court further stated in the said paragraph that if the earlier patent is in relation to broad Markush structure, it does not necessarily follow that a specifically filed patent application for an invention for a narrower claim is disclosed in the earlier patent. This decision was in the context of anticipation by prior claiming of a later filed patent for a specific compound being anticipated by an earlier granted patent for a Markush structure.

Novartis vs. Natco, C.S. (Comm) 256/2021 of December 13, 2021

The applicant submitted that the Defendant attempted to demonstrate anticipation by prior claiming of a granted patent for a species being contained in an earlier granted Markush claim. The Hon'ble Judge in the said case with regard to prior claiming in in **paras 34.2, 34.5, 34.6, 34.20 and 34.21** held as follows:

34.2 *Claim 1 of IN 161 specifically claims EO. The "invention" claimed in the claim in the complete specification of the suit patent is, therefore, EO. The suit patent can be rendered vulnerable to revocation under Section 64(1)(a), because of IN 161, only, therefore, if EO is claimed in a valid claim contained in the complete specification of IN 176.*

34.5 *Section 64(1)(a) envisages, as a ground for revocation of a patent, the circumstance that "the invention, so far as claimed in any claim of the complete specification, was claimed in a valid claim of earlier priority date contained in the complete specification of another patent granted in India".*

34.6 *The words "so far as claimed", in interpreting Section 64(1)(a), are, in my view, of paramount significance. By using the expression "so far as", the Legislature has made it clear*

*that Section 64(1)(a) would apply only where the extent to which an innovation is claimed in the complete specification of the patent under challenge is the same as the extent to which it is claimed in the prior art, on which the challenger places reliance. The claim, whose validity is being challenged, as it appears in the patent, **must be identical t**o the claim in the prior art, or of co-equal extent and amplitude.*

***34.20 Merck v. Glenmark** has made it absolutely clear that claim construction is to be based on the wording of the claim read with its enabling disclosures as contained in the complete specifications. Whether or not, a subsequent patent is vulnerable to revocation on the ground of anticipation by prior claiming would, therefore, have to be examined by comparing the claims, construing them by applying these principles. In **Merck v. Glenmark,** however, it is clarified that, in construing the claim in a patent, one is not to refer to any declaration or representation made prior to the grant of the patent or subsequent thereto.*

***34.21** Declarations in Form 27s cannot, prima facie, constitute a basis for asserting anticipation by prior claiming where, on its plain reading, the claim of the invention, so far as claimed in the suit patent, is not claimed in the prior art. The fact that, in the Form 27s which may have been filed in respect of the prior art, after the suit patent was granted, the product emerging from the suit patent was cited, cannot lead to a conclusion of anticipation by prior claiming.*

The applicant argued that the claims of IN 229051 do not render the subject matter of the present invention IN 4412 as being anticipated by prior claiming for the following reasons:

a. It is the case of the Plaintiff (Novartis) that the supramolecular complex of Valsartan and Sacubitril is not specifically claimed in the IN229051 patent. Claim 1 of the IN229051 patent has been interpreted as **(Para 38 & 44** of NOVARTIS AG & ORS vs NATCO & ORS, DHC, *enclosed as Annexure 11*).

38. A reading of Claim I shows that it comprises of composition of (i)Valsartan or a pharmaceutically acceptable salt; (ii) Sacubitril or a pharmaceutically acceptable salt; and a composition of pharmaceutically acceptable carrier.

44. Hence, merely because the plaintiffs have filed an application for registration of a supra molecular complex of the two components of Valsartan and Sacubitril being application No.4412 does not modify or change the position vis-a-vis interpretation of Claim 1 of the suit patent. Prima facie, there is no merit in, the said plea of the defendant.

The applicant further submitted that D1 is the patent for a combination of valsartan and sacubitril in a pharmaceutical composition and is the basic patent.

c. One of the main distinguishing features of the present invention with respect to D1 is that the present invention is directed to a single dual acting compound whereas D1 is directed to a composition comprising a combination of (a) AT-1 antagonist valsartan or a salt thereof, and (b) a NEP inhibitor, in particular (2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester or a salt thereof.

d. In D1, there is no reference whatsoever to a single dual-acting compound (unique novel compound) that combines two active ingredients by two different modes of action having an intricate network and stabilized by an involved network of ionic, hydrogen and/or coordination bonds, which has been described in various ways in the specification of the subject application.

e. It is submitted that D1, for the first time, disclosed the beneficial effect of a combination of valsartan and sacubitril in hypertension and cardiovascular related disorders. As such, D1 remains the basic patent for any kind of combination involving valsartan and sacubitril. However, it does not preclude the inventors from making further research and improve upon the basic invention as disclosed in D1. This is also recorded by Justice Jayanth Nath C.S (Comm) 62/2021 that states as follows in para 9

"It is further urged that after filing of the patent application, plaintiff No. 1 continued with additional experimentation. After much research, plaintiff No. 1 arrived at a supra molecular structure (or supra molecular complex) of Valsartan and Sacubitril. It is urged that the said supra molecular structure is a novel compound wherein two anionic components of Valsartan and Sacubitril together with sodium cations and water molecules are linked together non-covalently to form a single large and highly intricate supra molecular structure.

The applicant further submitted that research continued after D1 that is for a combination of two actives as claimed and with additional experimentation led to a new invention for a single dual acting compound that led to an invention which is the subject matter of IN 4412.

The applicant argued that D1 does not describe:

a) supramolecular compounds, complexes or co-crystals.

b) **single compound:** in the present invention valsartan and sacubitril are constituents of a single defined compound, whereas in D1 the chemical relationship between the individual active substances valsartan and sacubitril is left open.

c) **molar ratio of 1:1:** in the present invention, Valsartan and Sacubitril are provided in the particular molar ratio of 1:1, whereas the ratios of Valsartan and Sacubitril is left open in D1 / D1A, WO'345 (see, for instance, WO'345, page 15, 2nd para)..

The agent for applicant argued that Indian Patent Application No. 5434/DELNP/2007 (IN'5434) has a priority dat of February 11, 2005 and was earliest published (PCT publication date) on August 17, 2006. IN '5434 is clearly not a prior art as it was published after the priority date of IN '4412 application, which are as follows: (a) 60/735,093 (09/11/2005); (b) 60/735,541 (10/11/2005); (c) 60/789,332 (04/04/2006); (d) 60/822,086 (11/08/2006).

The agent for applicant further argued that In order to avail the ground of priority claiming u/s 13(i)(b) and 25(i)(c) of the Indian Patent Act, the following criteria have to be satisfied:

a) Only the claims have to be looked for the purpose of prior claiming and the description cannot be looked into
b) Object of prior claiming is to prevent double patenting, Therefore, clearly it does not apply for abandoned cases published after the priority date of the invention.

c) Further for prior claiming to be established what has to be seen is that the subject matter of the matter filed an application is **claimed** in an individualized claim of the earlier file application and in this regard, reference was made to the decision of ***Daikin Kogyo Co. Ltd. (Shurgu s) Application, [1974] RPC 559***

The applicant submitted that IN '5434 discloses a combination of either:

a) a renin inhibitor and a neutral endopeptidase (NEP) inhibitor or

b) a triple combination of a renin inhibitor, a neutral endopeptidase (NEP) inhibitor and an angiotensin II receptor blocker (ARB)

c) a triple combination of a renin inhibitor, a neutral endopeptidase (NEP) inhibitor and a diuretic. Thus, in any kind of combination covered by the claims of IN '5434, **a renin inhibitor is an essential ingredient and valsartan is not a renin inhibitor**.

The applicant argued that IN 5434 does not envisage even a composition consisting of Valsartan and Sacubitril let alone a compound as claimed in the present application. Thus, IN '5434 does not prior claimed the instant application, IN '4412.

Section 25(1) (e)-Obviousness/lack of inventive step

The opponent 2 (Natco Pharma Ltd.) **argued** that amended claim 1 recites a compound comprising the Angiotensin Receptor Antagonist valsartan and the NEP Inhibitor (2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2- methyl-pentanoic acid ethyl ester having the formula [((S)-N-valeryl-N-{[2'-(1 H-tetrazole-5- yl)-biphenyl-4-yl]-methyl}-valine) ((2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)- 2-methyl-pentanoic acid ethyl ester)]Na1-3 • x H2O, wherein x is 0 to 3. Dependent

claims recite the various solid forms of the compound of claim 1, particularly claim new claim 4 which recites that the compound is crystalline in nature. Claims 6 to 8 recite the method of preparation.

The opponent 2 submitted that the claimed compound is a Supramolecular complex, which has been defined in the specification as under,

The opponent 2 further argued that *the present invention, the term "supramolecular complex" is intended to describe an interaction between the two pharmaceutically active agents, the cations and any other entity present such as a solvent, in particular water, by means of noncovalent, intermolecular bonding between them. This interaction leads to an association of the species present in the supramolecular complex distinguishing this complex over a physical mixture of the species.*
The noncovalent intermolecular bonding can be any interactions known in the art to form such supramolecular complexes, such as hydrogen bonding, van der Waals forces and π-π stacking. Ionic bonds can also be present. Preferably, there exists ionic bonding and additionally hydrogen bonding to form a network of interactions within the complex. The supramolecular complex exists preferably in the solid state but may also be present in liquid media. ***As a preferred embodiment of the invention, the complex is crystalline and in this case is preferably a mixed crystal or co-crystal.***

In para 26 page 14 in his reply dated 20 september 2022 opponent pointed that According to the claimed invention the compound comprises
a) valsartan,
b) sacubitril, and
5 c) sodium cations at a molar ratio of 1:1:3.
d) The compound may further contain water molecules, and has a hydration state defined in the claims by "x", which is 0-3 in claim 1 , such as 0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 1, 2.25, 2.5, 2.75, or 3 (p. 22 second to last paragraph and p. 23).

Further in para 27- 29 the opponent argued that the molar content of water in the compound, it can either be in anhydrate form or a hydrate form.
The opponent 2 (Natco Pharma Ltd **)argued** that "***It is imperative that while the compound as recited in claim 1 can comprise 0-3 molecules of H20, in other words the compound can be both anhydrate and hydrate, the Applicant's claims thus encompassing anhydrate forms as well – no clarity if such forms would have the same properties as the hemipentahydrate."***
In this context reference is made to the following pleadings from the Reply Statement and opinion of the inventor, Dr Piotr H. Karpenski which has been relied upon by Dr. Dhandla in his affidavit filed on August 9, 2022.

The opponent 3 &6 (Kumar Sushobhan & G. Sriniwas Rao) submitted that the claims of the impugned application lack inventive step and are obvious and as such, no patent can be granted in respect thereof. There are various developments that took place in the prior art which would demonstrate that the claims of the impugned application are obvious.

WO2003/059345 relates to a pharmaceutical composition comprising a combination of (i) the AT 1- antagonist **valsartan or a pharmaceutically acceptable salt thereof** and (ii) a **NEP inhibitor or a pharmaceutically acceptable salt thereof** and optionally a pharmaceutically acceptable carrier and to a method for the treatment or prevention of a condition or disease selected from the group consisting of **hypertension, heart failure such as (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy,** etc.

WO345 discloses in third paragraph on page 2 that *"The nature of hypertensive vascular diseases is multifactorial. Under certain circumstances, APIs with different mechanisms of action have been combined."*

The opponent 3 &6 (Kumar Sushobhan & G. Sriniwas Rao) submitted : among the candidates of NEP inhibitors**, Sacubitril (N-(3-carboxy-1- oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester),** has been discussed specifically in second last paragraph on page 6 and in in-vivo studies on page 9 to 12, and in claims.

The invention of **WO345 pertains to and claims a composition of Valsartan and Sacubitril**, which are to be **administered together** or sequentially or simultaneously.

With regard to Sacubitril, it is stated in second last paragraph on page 6 that "*With respect to N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4- amino-2R- methylbutanoic acid ethyl ester,* ***preferred salts include the sodium saltdisclosed in U.S. Patent No. 5,217,996***". Therefore, among the known salt forms, the inventors of WO345 have selected sodium salt as the preferred salt form of Sacubitril.

Second paragraph on page 13 discloses that *"**In this composition, components (i) and (ii) can be obtained and administered together**, one after the other or separately in one combined unit dose form or in two separate unit dose forms. **The unit dose form may also be a fixed combination**.,* wherein (i) and (ii) refers to Valsartan and Sacubitril.

First paragraph on page 14 states that *"**A therapeutically effective amount of each of the componentof the combination** of the present invention may be **administered simultaneously**" and second paragraph on page 14 states that "The **corresponding active ingredient or a pharmaceutically acceptable salt thereof may also be used in form of a hydrate**"*

With regard to technical advancement and efficacy, WO345 states in second last paragraph on page 7 that *"It has surprisingly been found that, a **combination of valsartan and a NEP inhibitor achieves greater therapeutic effect than the administration of valsartan, ACE inhibitors or NEP inhibitors alone** and promotes less angioedema than is seen with the administration of a vasopeptidase inhibitor alone. **Greater efficacy can also be documented as a prolonged duration of action**."*

1. Furthermore, it is stated in last paragraph of page 7 that "***Further benefits are that lower doses of the individual APIs to be combined according to the present invention can be used to reduce the dosage, for example, that the dosages need not only often be smaller but are also applied less frequently, or can be used to diminish the incidence of side effects***. *The combined administration of valsartan or a pharmaceutically acceptable salt thereof and a NEP inhibitor or a pharmaceutically acceptable salt thereof results in a*

significant response in a greater percentage of treated patients, that is, a greater responder rate results, regardless of the underlying etiology of the condition."

2. WO345 discloses that **anti-hypertensive effect was studied in animal models: DOCA salt hypertensive rats and SHR rat model**. In the results it was observed that the dose required was decreased as stated in line 9 and 10 of first paragraph on page 12 *"**In combination, lower dosages of each agent are used** and correspondingly, valsartan is given in the range of 1 to 30 mg/kg/day and N- (3-carboxy-1 -oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R- methylbutanoic acid ethyl ester in dosages below 50 mg/kg/day."*

3. Further, fourth paragraph on page 12 states that *"The available results indicate an unexpected therapeutic effect of a combination according to the invention."*.

4. Therefore, WO345 teaches PSITA that a combination of valsartan with sacubitril results in better efficacy in terms of higher reduction in hypertension as compared to when valsartan or sacubitril are given alone to the patient.

5. It teaches that when the two APIs, Valsartan and Sacubitril, are given together, the dose of the APIs and the frequency of administration is reduced.

6. It is also disclosed that among known salt forms, Sacubitril sodium is the preferred salt form to be used in the invention.

Opponent 4 (Dr. Reddy's Laboratories Ltd.) submitted that the present application fails to establish any technical advancement in the field of the art, whatsoever. It is submitted that there was sufficient motivation for a person skilled in the art to arrive at the complex sought to be patented. Further, it is submitted that, having known and being used, the present application does not meet any requirement or need in the art as such. **.**

Opponent 4 (Dr. Reddy's Laboratories Ltd.) further submitted that **D1 (WO 2003/059345** – granted in India as **IN 229051;** expiring on 16/01/2023) is directed to a pharmaceutical composition comprising a combination of (i) the AT1-antagonist valsartan or a pharmaceutically acceptable salt thereof and (ii) a NEP inhibitor or a pharmaceutically acceptable salt thereof and optionally a pharmaceutically acceptable carrier.

The applicant argued at *the time of hearing that the patent specification has extensively demonstrated that the invention according to IN'4412 application relates to a **supramolecular compound** comprising two active ingredients/ moieties (a) an angiotensin receptor blocker (Valsartan), (b) neutral endopeptidase inhibitor (Sacubitril), whereas the invention according to WO'345 is a combination of Valsartan and Sacubitril.*

a) The claimed compound according to IN'4412 is unique and novel and comprises:

a. anionic Valsartan,

b. anionic sacubitril, and

c. tri sodium cations. The two actives and anionic are present in a precise stoichiometric ratio, preferably in the ratio of 1:1:3

d. The compound may further contain water molecules and has a hydration state defined in the claims by "x", which is 0-3 in claim 1, such as 0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 1, 2.25, 2.5, 2.75, or 3 (p. 22 second to last paragraph and p. 23). The hydration state of the said compound is a very small/ narrow range.

e. The compound is stabilized by non-covalent interactions (including hydrogen bonds, ionic bonds and van der Waals forces).

The applicant argued that Section 2(1)(ja) of the Indian Patents Act defines inventive step as "a feature of an invention that involves technical advance as compared to the existing knowledge or having economic significance or both and that makes the invention not obvious to a person skilled in the art"

The applicant further argued that "the present invention demonstrates several technical advantages/ advancements including economic significance as stated in paras 35-37 above and is not being reproduced again so as to avoid repetition. As stated in the affidavit of Dr. Michael Motto the new and unique compound of the present invention was arrived after extensive experimentation which is not a routine experimentation (**para 8 of Dr. Motto's affidavit; Please also refer to paras 32-34 above of the written submissions**)"

In addition to the fact that hindsight is impermissible in an obviousness analysis, the legal concept of teaching away is well recognized in India (as stated in Fresenius Kabi Oncology Ltd vs Glaxo Group Limited- Order 162/2013 in ORA/17/2012/PT/KOL) while determining the issue of obviousness. Further, in considering whether an invention is obvious, the Controller should look at the cited art as a WHOLE to consider whether the prior art as described in the references teaches away or motivates the person skilled in the art to not try the solution claimed in the patent application.

The opponent 2 (Natco Pharma Ltd.) submission and arguments

The opponent 2 argued that **It is imperative that while the compound as recited in claim 1 can comprise 0-3 molecules of H20, in other words the compound can be both anhydrate and hydrate, the Applicant's thus encompassing anhydrate forms as well – no clarity if such forms would have the same properties as the hemipentahydrate.**
In this context the opponent relies on the the Reply Statement and opinion of the inventor, Dr Piotr H. Karpenski.

Dr. Piotr H. Karpenski statements during the prosecution of the corresponding US Application, wherein he states as under. This is all the more pertinent since in US the Applicant filed in respect of the US counterpart US8877938 one affidavit of Piotr H. Karpenski wherein it is stated that - "*Under my direction and supervision, working diligently, over 1000 separate experiments were initially required to prepare, purify and characterize substantially pure trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3- ethoxycarbonylD1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate. The procedure to prepare , purify and characterize this compound was non-routine and required and undue level of experimentation*"***Many of the compounds which were isolated***

in the experiments were not sufficiently stable to be characterized and as such, they were considered poor candidates for further development. "

The opponent 2 ***submitted*** *that the claimed compounds are unique compounds wherein the two anionic components (Valsartan and Sacubitril) together with sodium cations and water molecules are linked together with non-covalent bonds to form a single large and highly intricate supramolecular structure. (***paragraph 8 of Reply Statement)**

The opponent 2 mentioned that Dr. Piotr H. Karpenski statements during the prosecution of the corresponding US Application, wherein he states as under. This is all the more pertinent since in US the Applicant filed in respect of the US counterpart US8877938 one affidavit of Piotr H. Karpenski wherein it is stated that -

"Under my direction and supervision, working diligently, over 1000 separate experiments were initially required to prepare, purify and characterize substantially pure trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3- ethoxycarbonyl˙1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2''- (tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate. The procedure to prepare , purify and characterize this compound was non-routine and required and undue level of experimentation. ***Many of the compounds which were isolated in the experiments were not sufficiently stable to be characterized and as such, they were considered poor candidates for further development. "***

The opponent 2 argued on Expert Affidavits and submitted that Dr. Michael Motto in paragraph 11 states that

In the absence of any feasible crystalline material, an amorphous dual-acting compound – although less desirable – was considered to be an acceptable resolution.

The opponent 2 further submitted that Further in paragraph 17, he states that

As it transpires from the above, the research route to form a double salt with monovalent cations seemed scientifically non-viable and counter-intuitive, but eventually led to the formation of the LCZ696 compound. The LCZ696 compound is fundamentally different from a physical mixture of valsartan and sacubitril sodium salts. Its crystal structure is described in L. Feng et al., *Tetrahedron Letters*, 53 (2012), 275–276, **Annexure "B"**.

The opponent 2(Natco Pharma) **submitted that "***the drug product of the compound, LCZ696 is a specific form and contains 2.5 degrees of hydration. Thus, the anydrate form which is claimed in the impugned patent admittedly unacceptable and less desirable. The entire evidence of* ***Dr Motto*** *is based on discovery of an unusual compound - LCZ969 which is a specific crystalline, supramolecular complex. He in fact emphasizes on the fact how multiple rounds of experimentations were required and the other forms were not found to be stable and not desired."*

The opponent 2(Natco Pharma **) relies on the** European Application, and submitted that the Applicant chose to limit to the particular compound when the Examiner objected that the claims were directed at a mixture and not a specific form (Office action dated 31.08.2009) in **EP1948158** (page 116 of compilation submitted by Opponent on 06.01.2020).
The opponent 2(Natco Pharma) **submitted** that during the Indian prosecution, the Applicant deleted the claims directed to such crystalline form in order to overcome the objections raised in the First Examination Report as seen it the **Applicant"s Written Submissions filed on May 30, 2016**. And the affidavits of **Dr. Allan S. Myerson and Dr. Gauri Billa** reinforces that the claimed compound is nothing but **a crystalline form of a known combination.**

The opponent 2(Natco Pharma) submitted that COMBINATION OF VALSARTAN AND NEP INHIBITORS AND ITS EFFICACY KNOWN IN THE ART. The Opponent relies on the cited document *D1 (WO03/059345) which is as Entitled pharmaceutical compositions comprising valsartan and NEP inhibitors.* The opponent submitted that **D1** at page 2 discloses that, "the nature of hypertensive vascular diseases is multifactorial. Under certain circumstances, drugs with different mechanisms of action have been combined. However, just considering any combination of drugs having different mode of action does not necessarily lead to combinations with advantageous effects. Accordingly, there is a need for more efficacious combination therapy which has less deleterious side effects."
The opponent 2(Natco Pharma) **submitted that , the problem solved by both D1 and the alleged invention is the same.**
The opponent mentioned page 9 as *((S)-N-valeryl-N-{[2'-(1H-tetrazole-5-yl)-biphenyl-4-yl]-methyl}-valine) and ((2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester.*

Further the opponent 2 mentioned page 6 for refrence and citation as D1 discloses that, ***"The compounds to be combined can be present as pharmaceutically acceptable salts. If these compounds have, for example, at least one basic center, they can form acid addition salts. Corresponding acid addition salts can also be formed having, if desired, an additionally present basic center. The compounds having at least one acid group (for example COOH) can also form salts with bases. Corresponding internal salts may furthermore be formed, if a compound comprises e.g. both a carboxy and an amino group." (Page 6)***

The opponent 2(Natco Pharma) **submitted that D1 discloses** that for N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4- amino-2R-methylbutanoic acid ethyl ester, preferred salts include the **sodium salt** disclosed in U.S. Patent No. 5,217,996. D1 discloses further salts that may be formed. *(Page 6)*

"It has surprisingly been found that, a combination of valsartan and a NEP inhibitor achieves greater therapeutic effect than the administration of valsartan, ACE inhibitors or NEP inhibitors alone and promotes less angioedema than is seen with the administration of a vasopeptidase inhibitor alone. Greater efficacy can also be documented as a prolonged duration of action. The duration of action can be monitored as either the time to return to baseline prior to the next dose or as the area under the curve (AUC) and is expressed as the product of the change in blood pressure in millimeters of mercury (change in mmHg) and the duration of the effect (minutes, hours or days). Further benefits are that lower doses of the individual drugs to be combined and can be used to reduce the dosage, for example, that the dosages need not only often be smaller but are also applied less frequently, or can be used to diminish the incidence of side effects. The combined administration of valsartan or a pharmaceutically acceptable salt thereof and a NEP inhibitor or a pharmaceutically acceptable salt thereof results in a significant response in a greater percentage of treated patients, that is, a greater responder rate results,
regardless of the underlying etiology of the condition. It can be shown that combination therapy with valsartan and a NEP inhibitor results in a more effective antihypertensive therapy (whether for

malignant, essential, renovascular, diabetic, isolated systolic, or other secondary type of hypertension) through improved efficacy as well as a greater responder rate. ” (Page 7)

It can be shown that combination therapy with valsartan and a NEP inhibitor results in a more effective antihypertensive therapy (whether for malignant, essential, reno-vascular, diabetic, isolated systolic, or other secondary type of hypertension) through improved efficacy as well as a greater responder rate. ***The combination is also useful in the treatment or prevention of heart failure such as (acute and chronic) congestive heart failure,*** *left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter or detrimental vascular remodeling.*

The structure of the active agents identified by generic or tradenames or code nos. may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, e.g. Life Cycle Patents International (e.g. IMS World Publications). The corresponding content thereof is hereby incorporated by reference. Any person skilled in the art is fully enabled to identify the active agents and, based on these references, likewise enabled to manufacture and test the pharmaceutical indications and properties in standard test models, both in vitro and in vivo. *(Page 8)*

The opponent 2(Natco Pharma) **submitted that DOCA test (pages 9 to 12)**

In combination, **lower dosages of each agent are used and correspondingly,** valsartan is given in the range of 1 to 30 mg/kg/day and N-(3-carboxy-1 - oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester in dosages below 50 mg/kg/day. However, in cases wherein the responder rate is increased with combination treatment, the dosages are identical to those used as monotherapy.

The available results indicate an unexpected therapeutic effect of a combination according to the invention. *(Page 12)*

In this composition, components (i) and (ii) can be obtained and administered together, one after the other or separately **in one combined unit dose form** or in two separate unit dose forms. The unit dose form may also be a fixed combination. *(Page 13)*

Pharmaceutical preparations for enteral or parenteral administration are, for example, in unit dose forms, such as coated tablets, tablets, capsules or suppositories and also ampoules. These are prepared in a manner which is known per se, for example using conventional mixing, granulation, coating, solubulizing or lyophilizing processes.
Thus, pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipients, if desired granulating a mixture which has been obtained, and, if required or necessary, processing the mixture or granulate into tablets or coated tablet cores after having added suitable auxiliary substances. *(Page 15).*

Pharmaceutical preparations for enteral or parenteral administration are, for example, in unit dose forms, such as coated tablets, tablets, capsules or suppositories and also ampoules. These are prepared in a manner which is known per se, for example using conventional mixing, granulation, coating, solubulizing or lyophilizing processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipients, if desired granulating a mixture which has been obtained, and, if required or necessary, processing the mixture or granulate into tablets or coated tablet cores after having added suitable auxiliary substances. *(Page 15)*

Valsartan is supplied in the form of suitable dosage unit form, for example, a capsule or tablet, and comprising a therapeutically effective amount, e.g. from about 20 to about 320 mg, of valsartan which may be applied to patients. The application of the active ingredient may occur up to three times a day, starting e.g. with a daily dose of 20 mg or 40 mg of valsartan, increasing via 80 mg daily and further to 160 mg daily up to 320 mg daily. Preferably, valsartan is applied once a day or twice a day in heart failure patients with a dose of 80 mg or 160 mg, respectively, each. Corresponding doses may be taken, for example, in the morning, at mid-day or in the evening. Preferred is q.d. or b.i.d.administration in heart failure.

In case of NEP inhibitors, preferred dosage unit forms are, for example, tablets or capsules comprising e.g. from about 20 mg to about 800 mg, preferably from about 50 mg to about 700 mg, even more preferably from about 100 mg to about 600 mg and even more preferably from about 100 mg to about 300 mg, administered once a day.

The opponent 2(Natco Pharma) **submitted that** ***D1 DISCLOSES PHARMACEUTICAL COMBINATIONS*** *comprising* ***VALSARTAN*** *(or pharmaceutically acceptable salts) and* ***SACUBITRIL*** *(or a pharmaceutically effective salts thereof) optionally in the presence of a pharmaceutically acceptable carrier and pharmaceutical compositions comprising them.*

- ***VALSARTAN*** *and* ***SACUBITRIL*** *administered together, one after the other or separately in ONE COMBINED UNIT DOSE FORM or in two separate unit dose forms. The unit dose form may also BE A FIXED COMBINATION. [page 13 of D1]*

- *VALSARTAN AND SACUBITRIL IN COMBINATION results indicate AN UNEXPECTED THERAPEUTIC EFFECT of the combination according to the invention.*

Opponent 4 (Dr. Reddy's Laboratories Ltd.) submitted that D1 teaches that NEP inhibitor is preferably N-(3- carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester being sacubitril or a pharmaceutically acceptable salt thereof; and that the preferred salt of sacubitril is sodium salt.
(reference: page 2, para 3 of document D1)
(reference: page 6, para 5 of document D1)

Opponent 4 (Dr. Reddy's Laboratories Ltd.) submitted that D1 also discloses that the combination of valsartan and sacubitril achieves better therapeutic effect than administration of valsartan alone or sacubitril alone.
(reference: page 7, para 3 and para 4 cont. on page 8 of document D1)(reference: page 12, para 4 of document D1) (reference: page 13, para 2 of document D1) (reference: page 14, para 1 of document D1)

The opponent 8 (KETAKEE S. DURVE) Submission and Arguments on WO 2003/059345 –IN 229051

Opponent no 8 Argument (1) on inventive step :

The opponent no 8 argued that the claims of D1A, demonstrating that a product comprising both valsartan and sacubitril is specifically claimed in these prior art documents. Therefore, the combined use of valsartan and sacubitril is clearly taught/disclosed in D1A. While this is not disputed by the patent applicant in its reply, out of abundant caution, reference may be had to:

(a) Internal page 3, which discloses valsartan;
(b)internal page 3, which teaches the combined use of valsartan along with the NEP inhibitor;
(c) internal page 5, lines 1-5 of D1A, which discloses sacubitril as the preferred NEP inhibitor, as well as claim 3 of D1A that also lists sacubitril as a preferred NEP inhibitor;
(d)Claim 1 and claim 3 of D1A.

The opponent no 8 submitted that the patent applicant has placed significant emphasis on the fact that D1A is only talking about two separate compounds which are merely brought together in the physical form as a composition. The patent applicant emphasises that this is very distinct from the supramolecular structure of the claimed invention because it is no longer two separate chemical compounds, but a single unified compound having dual action. This argument is wholly perverse for the following reasons:

(a) The person skilled in the art would appreciate that the purported supramolecular structure mentioned in claim 1 of the subject application is merely one mode of carrying the active ingredients. In its actual industrial applicability, i.e., to be ingested as a drug, the complex will no longer remain a complex in vivo. Instead, the complex will break down and result into its two separate active ingredients.

(b)It is also a matter of known science, as on the priority date of the invention, that valsartan has its own mechanism of action as an antihypertensive. Similarly, sacubitril's chemistry and function are known. Sacubitril is not sold separately as a drug; from D1A, the combination of valsartan and sacubitril (or their respective salts) is known. It is not as if the format of ingestion, i.e., whether as two separate chemical compounds in one physical carrier versus the tow compounds put together in a single molecule as a complex, has any relevance to the mechanism of action of the molecules in vivo.

(c) In other words, at best, the complex claimed in the subject application is the pro-drug for the composition disclosed and claimed in D1A.
(d)Accordingly, merely using one mode of combining these two molecules into a single molecule through complex formation cannot provide any inventive step. This is more so because complex formation is something well-known in chemistry and, most certainly, in pharmaceutical chemistry. It is not as if the subject application discloses any specific technical obstacles to be overcome in the complex formation process deployed to make the claimed complex.

The Opponent no 8 futther submitted that D1A further discloses each of these active ingredients, i.e., valsartan and sacubitril, their salts, combination of their salts as well as hydrates. Reference may be had to:

(a) Internal page 3, which references "pharmaceutically acceptable salts thereof", both for valsartan and NEP inhibitor. The term "pharmaceutically acceptable salt" is commonly used in the art as a matter of common general knowledge, including sodium salt, in the eyes of the person skilled in the art. Notably, D1A's disclosure does not limit the term to any specific salts, and, thus, the teaching to the person skilled in the art is that all salts used in the pharmaceutical industry routinely can be employed and covered within the term;

(b)Internal page 3, which specifically and expressly incorporates by reference, US 5399578 in its "entirety". Said US 5399578, at Column 1, Lines 61-67 and Column 23, lines 9-15, expressly teaches the use of sodium salt of valsartan. Said US 5399578 at Column 25 Lines 10-15, also teaches that valsaratan salts can be obtained in the form of their hydrates.

(c) Internal page 5, which references “pharmaceutically acceptable salts thereof” while listing sacubitril as a NEP inhibitor;
(d)Internal page 6, paragraph 3 talks explicitly about the compounds in question being combined as harmaceutically acceptable salts;
(e) Internal page 6, paragraph 4 specifically teaches the use of sodium salt of sacubitril as the preferred salt in the context of NEP inhibitors; (f) Internal page 14, paragraph 2 expressly teaches the use of the active ingredients (valsartan and sacubitril) or their pharmaceutically acceptable salts “in form of hydrate or include other solvents used for crystallisation”.

The Opponent no 8 submitted that it is now well-settled in patent law that disclosure in a prior art document is to be appreciated by what is disclosed, not just by express words but also by implication. That which is the inevitable result of following the teachings in a prior art document is considered to be disclosed in said prior art document.
The Opponent no 8 submitted that the inevitable result outcome of following the teachings mentioned in the above referenced internal pages 3, 5, 6 and 14 would result in the claimed invention. In particular, if a sodium salt of valsartan along with sacubitril (free acid) is brought together in a suitable solvent commonly used in chemistry as a matter of common general knowledge, such as acetone, and then crystallisation is permitted to occur, the resultant substance will be a supramolecular complex of sacubitril and valsartan having sodium and water molecules.

The Opponent no 8 submitted that **document D1A** expressly also teaches the purported benefits of combining valsartan and sacubitril. Internal page 7, paragraph 3 to internal page 8, paragraph 2 teaches the person skilled in the art that putting these two compounds together achieves greater therapeutic effect than using them singly. Internal page 9 and internal page 11 also refer to animal testing for a combination of valsartan and sacubitril.

The Opponent no 8 submitted the difference between what inevitably flows from D1A and claim 1 of the subject application is that claim 1 expressly requires 3 sodium atoms and the water molecules can be in the range of 0 to 3. However, there are three reasons why this purported distinction is meaningless and irrelevant for the purpose of the present proceeding:

(a) First, it is undisputed that the subject invention is intended as a pharmaceutical product. The subject invention, when ingested, will split into valsartan and sacubitril, each having its own mode of action. To that extent, the sodium atoms and water molecules as presented in the claim are not essential features as far as the industrial application of the subject invention is concerned. As such, therefore, no inventive step can be gleaned from such non-essential features.

(b)Second, the complete specification of the subject application is totally silent on the relevance of the number of sodium atoms or water molecules in the complex. In fact, at internal page 22, lines 1-10 of the subject specification, vague and generic references are made to the number of water molecules. There is not even a whisper of basic lab experiments to specify why the claimed range of 0 to 3 water molecules has any relevance to the invention at all.

(c) Third, the complex formation will necessarily result in 3 sodium atoms. This is an inherent and inevitable feature of complex formation between valsartan sodium salt and sacubitril; the complex will not be stable otherwise, and chemistry abhors instability.

(d)In summary, therefore, the number of sodium atoms is a matter of inevitability from the disclosure of D1A, and the number water molecules in the complex is simply a matter of random and/or arbitrary choice of the patent applicant. A set of arbitrary choices, without the complete specification providing even a whisper of any hitherto unknown technical effect associated with such arbitrary choices cannot add to the alleged inventiveness of the claimed invention.

The opponent no 8 argued that claim 1 of the subject application lacks inventive step in view of D1A, read in the light of common general knowledge.

The opponent no 8 submitted that the patent applicant is to contend that the use of sodium salt of valsartan in the complex formation is not expressly disclosed, and instead, there is only a generic reference to "pharmaceutically acceptable salts" of valsartan in D1A. As already argued above, this is not an acceptable contention since sodium salts are commonly used pharmaceutical salts that are routinely employed in the pharmaceutical industry. Alternatively, reference is made to the document marked as D4, which expressly teaches valsartan sodium salt. D4 was published on 17.09.2003, just a few months after the publication of D1A, and is expressly disclosed as relating to valsartan and its salts.

The opponent no 8 further submitted that D4 teaches that there is a need for a more stable crystalline form of valsartan (paragraph 7), since such crystalline forms tend to have more advantageous properties (para 14-16). In this context, D4 states that the object of the invention in D4 is the preparation of a salt of valsartan selected from a specific group of salts, the 1st of which is sodium salt of valsartan (paragraph 9). In fact, D4 goes a step further and states that sodium salts of valsartan, especially in hydrated form of the preferred salts (para 12). D4 also states that the invention in that prior art relates to solvents and hydrates of such valsartan salts (para 19).

The opponent no 8 argued that it is equally important to note that when highlighting the advantages of the invention in that patent, i.e., D4, it is especially taught that the salts of valsartan (of which sodium is the preferred salt as per para 12), show increased bioavailability and exceptional physical stability (para 15). D4 further teaches the skilled person that these advantages result in a higher formulation quality (i.e., when using preferred valsartan salts such as valsartan sodium) which also enables economic advantages to be obtained (para 16). Further, D4 also teaches that salt hydrates are preferred because water molecules in the crystal structure increase overall stability (para 20). Therefore, even assuming but not conceding that D1A has certain gaps, D4 fills those gaps. D4 specifically relates to the same subject matter and, therefore, would be something a person skilled in the art would consider highly relevant. The express reference to sodium salts being the preferred salts and the fact that such salts of valsartan disclose better bioavailability and 12 exceptional physical stability are strong motivations for any person skilled in the art to combine **D1A with D4.**
The opponent no 8 argued that the patent applicant's argument during the oral hearing was that D4 teaches away from using sodium salt. This is not correct on facts. There is actually no "teaching away" from the sodium salts. **Thus, alternatively, D1A in combination with D4, read in the light of common general knowledge, destroys the inventive step of claim 1 of the subject application**.

The applicant (NOVARTIS AG.) Submission Arguments on WO 2003/059345 –IN 229051

The applicant submitted that **WO '345 discloses** a pharmaceutical composition comprising a **combination** of Valsartan and Sacubitril. However, the subject matter of the IN '4412 application differs from WO'345 in at least the following respects:

a) **Intricate network** in which anionic Valsartan, anionic Sacubitril, sodium cation and optionally water molecules interact in a networkofionic,hydrogen andcoordinationbonds.

b) **Molar ratio is 1:1:** In the invention, Valsartan and Sacubitril are provided in molar ratio of 1:1, whereas the ratios of Valsartan and NEP inhibitor which may be administered are left open in WO'345 *(see, for instance, WO'345, page 15, second §);*

c) **Administration together:** in the invention, Valsartan and Sacubitril are provided in a form that necessitates their administration together, whereas in WO '345 the physical relationship of the individual active substances Valsartan and Sacubitril is left open *(see, for instance, WO '345, page 13, second* §); and

d) **Single Compound:** Valsartan and Sacubitril are constituents of a single defined compound – a trisodium compound, which may contain 0-3 water molecules, preferably a trisodium hemipentahydrate compound - whereas in WO'345 the chemical relationship between the individual active substances Valsartan and Sacubitril is left open ***(see para 4.4 of Dr. Myerson's affidavit)***.

The applicant submitted *that there is no teaching in* WO '345 towards dual-acting compound (unique novel compound) that combines two active ingredients with two different modes of action having an intricate network and stabilized by an involved network of ionic, hydrogen and coordination bonds.

Para 4.4 of Dr. Allan Myerson's affidavit.

> 4.4 There is no disclosure in D1 of the claimed unique compound comprising the two components (valsartan and sacubitril) in their respective anionic form together with sodium cations and water molecules, linked together with non-covalent bonds to form a single large and highly intricate supramolecular structure. There is also no teaching or suggestion in D1 towards combining valsartan and sacubitril into a single supramolecular compound, and no indication of how such a compound could be made.

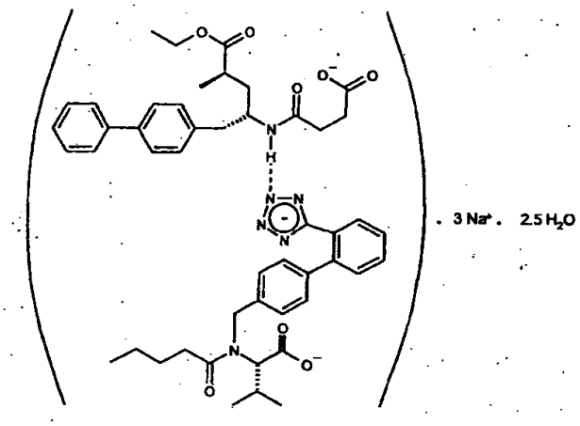
As stated in para 11 above, IN '4412 application relates to a **supramolecular compound** comprising two active ingredients/ moieties (a) an angiotensin receptor blocker (Valsartan), (b) neutral endopeptidase inhibitor (Sacubitril) and sodium cations in a precise stoichiometric ratio, preferably 1:1:3. The compound may optionally further contain water molecules and has a hydration state defined in the claims by "x", which is
0-3 in claim 1, such as 0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 1, 2.25, 2.5, 2.75, or 3 (*p. 22 second to last paragraph and p. 23*). The compound is a **single entity** that is stabilized by non-covalent interactions (including hydrogen bonds, ionic bonds and van der Waals forces).

The preferred embodiment in the IN '4412 is wherein "x" is 2.5, i.e., a hemipentahydrate and *(p. 22, second to last paragraph, of the specification of the 4412 Application*) is specifically claimed by claims 2 and 3 of the present application. The said embodiment is trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1- butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl- 4'-ylmethyl}amino)butyrate]-hemipentahydrate.

This preferred embodiment is exemplified in Examples 1-3 of the IN '4412 Application (pages 40-43 of the specification) and is fully characterized by various analytical and spectroscopic techniques (p. 24-29 and 43-45 of the specification). The therapeutic effect of the claimed compound has been confirmed in the representative animal studies performed and described in the specification of the IN '4412 Application (*p. 33-35 and paras 2.1 to 2.11 of Dr. Myerson's affidavit).*

a) The single crystal X-ray diffraction (SCXRD) data for the exemplified embodiment of the claimed supramolecular compound reveal a highly unusual and intricate three-dimensional structure, as summarized on page 28 of the specification of the IN 4412 Application.

b) A simplified structure of the said embodiment is shown below *(p.23 of the specification):*



The unique structural **feature of the preferred embodiment of the present invention:** The aforementioned preferred embodiment is a representative compound of the claimed invention known as LCZ696. LCZ696 (referred to herein as "LCZ696") is unique with a complex interaction of ionic and hydrogen bonding between Valsartan anions, Sacubitril anions, sodium cations and water. The asymmetric unit of the crystalline supramolecular complex consists of:

a) 6 molecules of Valsartan in its anionic form;

b) 6 molecules of Sacubitril in its anionic form;

c) 18 sodium cations,

d) 15 water molecules,

e) Monoclinic unit

f) molecular formula of $C_{288}H_{330}N_{36}O_{48}Na_{18}\cdot 15H_2O$ (M.W. 5748.03).

g) The sodium cations are coordinated by oxygen ligands derived from **twelve carboxylate groups** and **eighteen carbonyl groups** (in the Sacubitril anions and Valsartan anions), and from 13 of the 15 water molecules (*see page 29, 3rd para of the patent specification* of IN‘4412 application). The interactions are defined in the specification wherein the sodium cations are preferably coordinated to several oxygen ligands which come from carbonyl and carboxylate groups (*page 11, para 3 of the complete specification*).

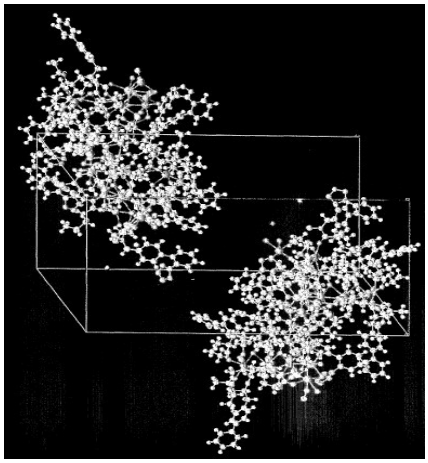
h) In all six of the Valsartan moieties, the tetrazole rings do not have an ionic bond directly to sodium, but instead form a hydrogen bond to the amide NH of the Sacubitril moieties; the amide carbonyl groups coordinate to the sodium ions. In addition, the tetrazole ring forms hydrogen bonds with water, which in turn forms part of the coordination polyhedra of the sodium ions. *(Feng et al., Fig.2).*

i) This **arrangement of sodium coordination is so efficient that each carbonyl and carboxy oxygen in both components is associated with multiple sodium ions**.

(Please refer to “interactions” as described in the specification and the Feng article submitted with affidavits of Dr. Allan S. Myerson & Dr. Michael Motto on June 6, 2020) as well as the patent specification of the IN’4412 Application@ page 24 and 29)

j) This interaction leads to an association that makes the compound distinct from a combination of ARB and NEPi obtained by simply physically mixing the two active agents. Thus, the compound has different physico-chemical properties that make it particularly useful for manufacturing and therapeutic applications (*pages 8, 11 and 24 last paragraph of the specification of the IN’4412 Application*).

k) The single crystal X-ray diffraction (SCXRD) data for the exemplified embodiment LCZ 696 of the claimed supramolecular compound reveal a highly unusual and intricate three-dimensional structure, *as summarized on page 28 of the specification of the 4412 Application.* A pictorial representation of the unit cell of the exemplified supramolecular compound, LCZ 696 comprising two asymmetric units is represented in *Fig. 1 of the IN 4412 Application*, and reproduced below:



Pictorial representation of the unit cell of LCZ696 *(page 29, paras 2-3 of the complete specification of the IN'4412 Application)*

l) The patent specification also illustrates the best method for performing the invention under Section 10(4) of the Indian Patents Act (*as examples 1-3*) by describing alternate methods for making the preferred embodiment described above in para 25.

m) *Dr Allan Myerson's affidavit at paragraph 3.1* states that the claimed supramolecular compound reflects an **unusual approach for drug development** in particular of 2 actives in anionic form linked via cationic linking- it required an **OUT OF BOX THINKING.**

Applicant(NOVARTIS AG.,)Submission on (US5217996)

(B) SUBMISSIONS OF THE APPLICANT: US5217996 (US '996) CITED IN THE SPECIFICATION OF IN 4412 PROVIDES NO RELEVANT TEACHING TOWARDS THE INVENTION; IT CANNOT BE TAKEN ON RECORD

US5217996 (US '996) was not cited by the Opponent in the Opposition and reference in relation thereto was made by the Opponent through the patent specification of IN 4412 that refers to the said document. These arguments in relation to US 996 cannot be taken on record as the Opponent has no pleadings in their opposition in relation to US 996. If the Opponent wished to rely on US 996, she should have at least made reference to the said document in the opposition statement and filed a copy of the said document, US'996.

Without prejudice to the above submissions as discussed in the previous oppositions, US 996 relates to NEP inhibitors having the structure of Biaryl substituted 4-amino-butyric acid amides. It discloses a number of NEP inhibitors including sacubitril. As stated earlier, it has also been identified in the background section of the present application. However, as mentioned

above, it is relevant to mention here that Sacubitril or its salts including its sodium salt have not been approved for human treatment so far (sacubitril has only ever been approved in the form of Vymada®; never separately). US996 does not refer to valsartan (or indeed any ARB)and there is therefore no teaching, suggestion or motivation directing the skilled person towards creating a supramolecular compound of valsartan and sacubitril.. Further, Example 8 of US '996 discloses preparation of sodium salt of Sacubitril capsules containing 50 mg of [N-(3-Carboxy-1-oxopropyl)- (4S)-p-phenyl phenyl methyl)-4-amino-2R-methyl butanoic acid, ethyl ester].

However, it is irrelevant that US '996 discloses a sodium salt of Sacubitril because US '996 does not disclose any combination of Sacubitril (or a sodium salt of Sacubitril) with Valsartan. US'996 therefore provides no relevant teaching towards the invention.
Even otherwise, POSA will become aware that sodium salt of Sacubitril is not good for further development as the said salt of Sacubitril is hygroscopic as shown below.

PROPERTY	LCZ696	VALSARTAN DISODIUM SALT	SACUBITRIL MONOSODIUM SALT
Hydration	2.5 H_2O	3 H_2O	anhydrous
Hygroscopicity (% at 60% relative humidity)	0.6	5	13
Hygroscopicity (% at 75% relative humidity)	6.9	6.5	26

The amount of absorbed moisture in a drug can influence the **flow and compression characteristics of powders** during manufacture and can have an impact on the hardness of final tablets and granulations.

Water absorption by APIs also frequently **affects the physical and/or chemical stability of final dosage** forms and always introduces serious content uniformity concerns. This will not motivate POSA to use monosodium salt of Sacubitril and there is a clear teaching away.

C) SUBMISSIONS OF THE APPLICANT: US5399578 (US '578) CITED IN THE SPECIFICATION OF IN 4412 PROVIDES NO RELEVANT TEACHING TOWARDS THE INVENTION; IT CANNOT BE TAKEN ON RECORD

US5399578 (US 578) was not cited by the Opponent in the Opposition and reference in relation thereto was made by the Opponent through the patent specification of IN 4412 that refers to the said document. These arguments in relation to US 578 cannot be taken on record as the Opponent has no pleadings in their opposition in relation to US 578. If the Opponent wished to rely on US 578, she should have at least referred to the said document in the opposition statement and filed a copy of the said document, US'578. This is clearly in violation of the law of pleading and the principles of natural justice.

Without prejudice to the above submissions as discussed in the previous oppositions, US 578 provides no relevant teaching to the invention. This document is in relation to the New chemical entity and disclosed thousands of compounds through the Markush structure and one such compound disclosed is Valsartan. The said document being a 1995 document is acknowledged as disclosing Valsartan by the applicant in the patent specification. In relation to the Na salt of valsartan, a person skilled in the art would be aware of WO 2002/006253 which is later to US 578 clearly shows that Na salt of valsartan is not a preferred salt as discussed herein below.

Applicant(NOVARTIS AG.,)Submission (CN1443176A) (CORRESPONDING TO WO2002/006253 WO '253), SUBMISSIONS OF THE APPLICANT: D4, CN1443176A (CORRESPONDING TO WO2002/006253 WO '253), TEACHES AWAY FROM SODIUM SALTS OF VALSARTAN

At the outset, the claimed compound is a new single compound and is distinct (separately patentable) from a mere physical mixture of sodium salts of valsartan and sacubitril. CN'176/WO'253 , which relates to simple salts of valsartan, provides no relevant teaching towards the present invention. In any event, valsartan, in an approved form (Diovan & Co-Diovan) is present as free acid, i.e. not as a salt, and this well-known free acid form would have been the obvious route for the person skilled in the art looking to develop valsartan.

The Applicant submits that there is no reference of any combination of Valsartan with Sacubitril in WO '253 let alone the compound claimed in the IN '4412 application.
Without prejudice to the above submission, a person skilled in the art would not have selected Valsartan disodium salt from WO '253 for various reasons as given below.

The law in relation to inventive step is that a teaching of a prior art has to be seen as a whole rather than cherry picking references arbitrary (*Roche vs CIPLA, RFA 92/2021, page 58, enclosed as Annexure 16*). WO '253 provides a laundry list of salts of Valsartan. However, a person skilled in the art (POSA) will read this document as a whole and upon reading the document recognize that calcium tetrahydrate and magnesium hexahydrate are "particularly preferred" due to their "exceptional physical stability" (*page 4, middle §; page 6, 5th paragraph; also, other "outstanding" properties on pages 7, 15 and 23*).

Further, WO '253 at pages 7, 15 & 23 clearly reports that the said two salts have water solubility several times better than that free acid of Valsartan, have high melting point and excellent chemical and physical stability and is suitable for pressing directly to form corresponding tablet formulation and has advantageous properties such as uniform crystal conglomerates which can be used in the galenic formulation.

Further, no such advantageous properties are attached to sodium salt – to the contrary sodium salt has poor physical properties.

a) Example 5 (page 47) describes disodium Valsartan as "hygroscopic".

b) Example 11 (page 51) describes a disodium Valsartan hydrate which is "slightly hygroscopic" and ill-defined stoichiometry (2.4 ± 1.0 moles).

. Thus, a person skilled in the art would be motivated to use the calcium/magnesium salt of Valsartan and not the disodium salt particularly when the said disodium hydrate salt of Valsartan is hygroscopic *(pages 47 & 52, §1)*. Further, the formulation example 1 and 2 disclosed in WO'253 at *pages 59 and 60* provide a tablet with calcium tetrahydrate and magnesium hexahydrate.

Also, *Dr. Michael Motto in para 17* states that during the research, the inventors recognized that to form a double salt with monovalent cations seemed scientifically non- viable and counter intuitive and therefore a person skilled in the art would not have selected a sodium cation to make a single compound containing Valsartan. [P.S Valsartan is a diprotic acid and therefore there was a clear teaching to a divalent salt (Ca or Mg)] instead of a monovalent salt (Na, K).

Therefore, a person skilled in the art would be motivated to use calcium tetrahydrate and magnesium hexahydrate and will be taught away from using a monovalent salt such as a sodium salt of Valsartan. This is notwithstanding the fact that in the present invention is in relation to a **single entity/ compound** of Valsartan and Sacubitril with trisodium cation.(*please see page 46 of the patent specification).*

SUBMISSION OF THE APPLICANT: NO MOTIVATION FOR A POSA TO ARRIVE AT THE COMPOUND CLAIMED IN IN '4412 FROM THE TEACHING OF D1A, WO '345 IN COMBINATION WITH COMMON GENERAL KNOWLEDGE

The Applicant respectfully submits that in the pharmaceutical field at the priority date, co-crystals formed between a neutral API molecule and a co-crystal former ("co-former") molecule were referred to as "pharmaceutical co-crystals" and were considered a new and unexplored class of materials at the priority date. A co-former was typically a structurally simple, neutral molecule that could act as an inert additive to assist in the formation of a crystal.

As reflected in the references cited in the previous opposition, and as explained by *Dr Myerson at paras 3.1-3.3,* the formation of pharmaceutical co-crystals involving an API and a co-former was

a) Unpredictable;

b) they were notusedasamatterofroutineindrugdevelopmentattheprioritydate c) Pharmaceutical co-crystals involving two APIs were even more unusual.

Indeed, at the priority date, there were no pharmaceutical designated supramolecular compounds containing two different active ingredients approved for heart failure or hypertension. Applicant's drug ENTRESTO/VYMADA containing the claimed compound is the **first ever** approved pharmaceutical supramolecular compound containing two active ingredients for the treatment of heart failure.

The Opponent has failed to provide any documents, be it a patent document or evidence of an expert to establish common general knowledge, that relates to a supramolecular compound comprising **two anionic moieties**, let alone two anionic APIs. The opponents have clearly used impermissible hindsight in their arguments.

THE DEVELOPMENT OF SUPRAMOLECULAR COMPOUND OF IN '4412 REQUIRED EXTENSIVE EXPERIMENTATION (NOT ROUTINE)

Dr. Michael Motto's affidavit clearly explains that various "experimental quests" were undertaken to combine Valsartan and Sacubitril into a single chemical entity ***(Para 3 of Dr. Michael Motto's affidavit)*** and that the formation of a single entity of two actives was challenging and not routine. This further goes to establish that the present invention is not obvious and requires extensive research.

Dr. Michael Moto highlighted the extensive experimentation and research that led to the development of claimed compound. Various strategies were attempted unsuccessfully:

a) Mixed Anhydride approach

b) N-Acyl Tetrazole approach

c) Imide approach

d) Crystalline double salt formation approach

The process to prepare the claimed compounds is **not routine** and developed after extensive experimentation and research (provides technological advancement). (***Paragraphs 3 to 17 of affidavit of Dr Michael Motto***).

SUBMISSIONS: THE TECHNICAL ADVANCEMENT/ ECONOMICAL ADVANTAGE UNDER SECTION 2(1)(J)(A)

The IN '4412 application provides the effects of both Valsartan and Sacubitril in a single compound which has several advantages:

a) One single compound comprising of both active ingredients inaratiowhich turnedouttobe thedesiredprecisestoichiometry at a fixed 1:1 molar ratio, is a **significant advantage**. **Novel single compound** comprising in which entities Valsartan and Sacubitril, in which entities are present in 1:1 stoichiometric ratio (*Gu et al filed with Dr. Motto's evidence*)

b) Both drug substances are present as a single compound which means that they will be simultaneously released after administration at the precise desired stoichiometry (useful for therapeutic applications) as opposed to WO '345 wherein the chemical relationship between the individual active *substances* Valsartan and Sacubitril is left open. (*see, for instance, p. 15, second paragraph*)

c) A single compound is simpler to formulate and manufacture. When two separate compounds are co-formulated in a single drug product, excipients must be

chosen which are compatible with each drug substance and the drug substances themselves must be chemically compatible when in physical contact.

The preferred embodiment in which x=2.5 (claims 2 and 3), exemplified by LCZ696, additionally possesses the following advantages:

a) LCZ696 compound possesses a set of superior physico-chemical properties such as crystallinity, low hygroscopicity, stability, and solubility and demonstrates improved bioavailability in comparison to the separate active ingredients (*page 8, 11 and 24 of the patent specification*)

b) **Economical advantage**: Less hygroscopic. *Reduced hygroscopicity is a key feature of the supramolecular compound which combines the constituents of the compound in a single crystalline phase.*

c) LCZ696 is very stable with no degradation being observed after 1 week at 50˚ C –both for LCZ696 alone and in the presence of excipients –either in sealed containers or under 58% relative humidity. *(Feng et al)*

d) These physiochemical properties enable development of LCZ696 as a potentially promising **novel active ingredient in pharmaceutical products.**

{Refer to affidavit of Dr. Michael Motto (Paras 18-21, 25); Affidavit of Dr. Allan S. Myerson (Para 6.1, 6.2, 4.5) and Feng et al.} chosen which are compatible with each drug substance and the drug substances themselves must be chemically compatible when in physical contact.

The preferred embodiment in which x=2.5 (claims 2 and 3), exemplified by LCZ696, additionally possesses the following advantages:

a) LCZ696 compound possesses a set of superior physico-chemical properties such as crystallinity, low hygroscopicity, stability, and solubility and demonstrates improved bioavailability in comparison to the separate active ingredients (*page 8, 11 and 24 of the patent specification*)

b) **Economical advantage**: Less hygroscopic. Reducedhygroscopicity isakey featureofthe supramolecularcompoundwhichcombinestheconstituentsofthe compoundinasinglecrystalline phase.

c) LCZ696 is very stable with no degradation being observed after 1 week at 50˚ C –both for LCZ696 alone and in the presence of excipients –either in sealed containers or under 58% relative humidity. *(Feng et al)*

d) These physiochemical properties enable development of LCZ696 as a potentially promising **novel active ingredient in pharmaceutical products.**

{Refer to affidavit of Dr. Michael Motto (Paras 18-21, 25); Affidavit of Dr. Allan S. Myerson (Para 6.1, 6.2, 4.5) and Feng et al.}

THE ADVANTAGEOUS PROPERTIES OF THE INVENTION IN PARTICULAR LCZ696 IS NOT PREDICTABLE.

The Applicant submits that that it is unpredictable at the priority date whether a single compound - in particular, supramolecular compound - of Valsartan and Sacubitril would have existed at all. Further, the advantageous properties of the exemplified compound LCZ696 mentioned above (a representative compound of claim 1) could not have been predicted at the priority date.

Therefore, it is established that the compound disclosed and claimed in the IN' 4412 application is inventive over the prior arts cited in the present opposition as it possesses technical advantage

and provides no teaching, suggestion or motivation to a person skilled in the art to arrive at the present invention WITHOUT hindsight, which is impermissible in an obviousness analysis.

The compound subject matter of '4412 application and in particular as claimed in claims 2 & 3 (e.g., LCZ696) is the active ingredient used in commercially successful drug product marketed under the brand Vymada/Entresto.

Commercial product: Entresto® is a successful commercial product. The unusual, inventive approach is confirmed by the remarkable fact that the Applicant's drug ENTRESTO/VYMADA containing the claimed compound is believed to be the **first ever** pharmaceutical supramolecular compound containing two active ingredients approved for the treatment of heart failure. The said drug product is **the first-in-class angiotensin receptor-neprilysin inhibitor (ARNi**), approved in India for the treatment of heart failure (HF).

As stated by ***Dr Gauri Billa in her affidavit*** at paras 7 to 9 LCZ696 is now a **class I recommendation** for patients of HFrEF by both the American and European Heart Failure Guidelines (2016). It is the first approved drug in the class of ARNi, which is a **breakthrough in chronic heart failure therapy** and has a **unique mode of action which acts to enhance the protective effects** of the Natriuretic Peptide (NP) system while simultaneously suppressing the harmful effects of an overactive Renin Angiotensin Aldosterone System (or RAAS). LCZ696/Vymada is a breakthrough drug, particularly, considering that it is the first drug developed and approved in the class of ARNi for treatment of heart failure using the inventive combination of Valsartan and Sacubitril. The said drug, therefore, has proven therapeutic efficacy which has hitherto unknown. Sacubitril was never previously approved or developed as a drug and even today has never been approved as a monotherapy.

Reference is made to the order of

a) Division Bench of the Delhi High court in Roche v/s Cipla, RFA (OS) 92/2012

Para 57. This argument ignores the fundamental truth about breakthrough inventions, which at the time they are invented may not be commercially the most viable for immediate marketing. They are useful and are industrially applicable as without them there would be no stepping stone to achieve the next lot of improvements.

The subject matter of the IN '4412 application has been granted patent in 70 countries.

In *particular, very similar claims have been granted by the EPO in divisional patent EP2340828B1 (EP '828)* ***(filed with the patent office and enclosing again as Annexure-17)***.

In particular, as in the pending claims of IN' 4412, the EPO divisional patent EP '828 claims the range x=0-3 and has a dependent claim to x=2.5. EP '828 claim 1 explicitly

claims x=0-3 in the solid form and therefore corresponds to claim 1 in India. EP '828 claim 7 explicitly claims x=2.5 and therefore corresponds to claim 2 in India. Given that the EPO has granted very similar claims in EP '828 covering x=0-3 and x=2.5, the opponent's objection should be rejected. In addition, we confirm that the EPO parent patent, EP1948158B1, (claim 1 of which is similar to claim 3 of 4412 application) was maintained as valid in post-grant opposition proceedings.

Reference is made to the IPAB order in **OA/53/2020/PT/CHN (copy enclosed as *Annexure 18*)** wherein the IPAB in state that

"The submission that the appellant has reveals that corresponding US and EP applications have been granted is an indication that the inventions were found to have passed the tests of inventive step in those jurisdictions"

SECONDARY CONSIDERATION OR OBJECTIVE INDICIA OF INVENTIVE STEP

The preferred embodiment of the IN '4412 application has led to the development of a commercially successful drug, Entresto/Vymada®. Besides the claimed invention fulfilling the criteria of patentability, the claimed compound also satisfies the criteria of secondary consideration.

a) Regulatory approval in 115 countries and launched in 100+ countries

b) Entresto® is a long-awaited **breakthrough** in the treatment of heart failure.

c) It is the first approved treatment for reduced ejection fraction heart failure in over ten years and is a **gamechanger** (Medpage Today, 5 Game-Changers in Cardiology in 2015: Entresto, see: http://www.medpagetoday.com/cardiology/chf/55415). [Para 9 of Dr. Gauri Billa's affidavit]

d) Clinical Trials in Entresto® 200 mg twice a day was stopped prematurely because of its **"overwhelming benefit"** (J.J.V. McMurray et al., The New England Journal of Medicine, 371 (2014), 993).

e) Entresto® is the first and only regulatory approval of Sacubitril. In other words, Sacubitril has not been approved till date as a monotherapy and was approved for the first time in Entresto®.

. In this regard, reference has been made to the case ***Roche v/s Cipla, RFA (OS) 92/2012, page 58, para 106, enclosed as*** *Annexure 16.*

Besides the primary consideration as noted, the objective indicia of non- obviousness include secondary considerations such as (i) a long-felt need; (ii) failure of others; (iii) industry acclaim; and (iv) unexpected results.

By Applicant (NOVARTIS AG.,) CONCLUSION ON OBVIOUSNESS

At the very outset, it is submitted that from D1/D1A, the Opponent has not made any argument as to how from D1 a person skilled in the art arrive at the present invention given that there was a clearly teaching away to arrive at a supramolecular compound. The Opponent has simply left the lack of inventive step argument open.

The Applicant submits that the Opponents has applied the hindsight approach in alleging that the cited documents together render the claimed compound obvious. None of these citations teach or suggest the formation of the claimed compound. At the priority date, a person skilled in the art would not have been motivated by the cited prior art to combine two APIs into one compound, let alone the anions of two specific APIs – Valsartan and Sacubitril – at a fixed 1:1 molar ratio together with sodium cations and optionally water molecules.

(a) <u>No direction, no motivation for POSA to arrive at claimed compound from WO '345</u>

There is no teaching, suggestion or motivation in WO '345 for a person skilled in the art to prepare a dual acting compound of the IN '4412 application (supramolecular compound) comprising Valsartan and Sacubitril with features referred to above in paras 15 to 18.

(b) <u>POSA would not have selected monosodium salt Sacubitril from US '996</u>

. **There is no scientific or legal basis for the Opponent to suggest that the claimed compound can be arrived at by "selecting" the monosodium salt of Sacubitril from US**

'996, which does not disclose any combination of Sacubitril (or its salts) with Valsartan (or its salts). In any event, POSA would not have selected the sodium salt when trying to make a single compound or when trying to solve the objective technical problem of providing an improved pharmaceutical composition for providing Valsartan and Sacubitril to patients allowing ease of formulation and manufacture, in particular demonstrating lower hygroscopicity.

Therefore, the skilled person would not have selected Sacubitril monosodium as the basis of an improved formulation, in particular having reduced hygroscopicity.

(c) **POSA would not have selected disodium salt of Valsartan from WO '253 or US' 578**

There is no scientific or legal basis for the Opponent to suggest that the claimed compound can be arrived at by "selecting" the disodium salt of Valsartan from WO'253, which does not disclose any combination of Valsartan (or its salts) with Sacubitril (or its salts). In any event, POSA would not have selected a sodium salt of Valsartan from WO '253 when trying to make a single compound or when trying to solve the objective technical problem without hindsight.

At the priority date, the only authorized form of Valsartan (in Diovan & Co-Diovan) was the **amorphous form of the free acid i.e. not as a salt**,

Moreover, WO '253 teaches the skilled person away from a sodium salt of Valsartan based on physical properties.

. Example 5 of WO '253 describes a disodium hydrate salt of Valsartan which is "hygroscopic" and example 11 describes a disodium hydrate salt of Valsartan which is "slightly hygroscopic" and having an ill-defined stoichiometry (2.4 ± 1.0 mole H2O). **High hygroscopicity and ill-defined stoichiometry** are properties that frequently lead to difficulties in formulation and manufacture of pharmaceuticals.

The teaching of WO '253 as a whole is towards calcium tetrahydrate and magnesium hexahydrate are "particularly preferred" due to their "exceptional physical stability" (*page 4, middle §; page 6, 5th paragraph; also, other "outstanding" properties on pages 7,15 and 23*).

(d) Formation of co-crystal was not routine at the priority date and nascent as on the priority date

At the priority date, in view of the documents cited in the previous oppositions, such as Almarsson and Morisette clearly demonstrate that co-crystals and supramolecular compoundswere:

a) **Not a routine technique** in pharmaceutical research and development.
b) Co-crystallization of two active pharmaceutical ingredients ("APIs") would have been considered even more **exotic and** extremely **unusual**.
c) Defied prediction

d) [That despite centuries of research the fundamental mechanisms and molecular properties that drive crystal form diversity, specifically the nucleation of polymorphic forms, are **not well understood** and therefore **predictive methods** for accessing behavior remains a **formidable challenge** *[Morissette et al at page 276, RHS, last para]*.

e) T**he prediction** of packing structures for multicomponent (e.g., solvates, hydrates, co-crystals) or ionic systems **is not yet possible** *[Morissette et al at page 277, LHS, first para]*.

f) *Morissette et al* further demonstrates unpredictability in the art: "*The existence and identity of hydrates, solvates, co-crystals and polymorphs have **defied prediction"*** and "*in general discrete crystal forms are considered **non-obvious and patentable"***.[*Morissette et al at page 296 (RHS, last para)]*

g) *Almarsson et al* states that pharmaceutical co-crystals "*represent a relatively **unexplored class of compounds***" *(p. **1890, page 1890, LHC, 1st §) and*** confirms that co-crystals were not a routine part of pharmaceutical research and development (***Para 4.20 of Dr Allan Myerson***).

'Pharmaceutical co-crystal' at the priority date referred to a co-crystal formed between **one active pharmaceutical ingredient** (API) and **one co-crystal former** (also referred to as a co-former) that is a solid under ambient conditions. *[Refer to Dr. Myerson affidavit para 3.1]*.

(e) The claimed compound was unprecedented

The claimed compound is unique.

It was counterintuitive to make a compound that contains two components in anionic form, let alone two APIs in anionic form. Clearly, the skilled person had no motivation to prepare such a compound and no reasonable expectation that such a compound could be made and would be useful in combination therapy. The Applicant's invention of the claimed compound is remarkable, as is reflected by the fact that it is the first ever approved pharmaceutical supramolecular compound containing two active ingredients for the treatment of heart failure.

Applicant (NOVARTIS AG .)Arguments and Submission on D1 :WO 2003/059345

The Applicant submitted that the specifications of IN '4412 and WO'345 (D1) are neither similar nor identical to each other as they both relate to two separate inventions. There is no disclosure or even a reference of the invention of including the claimed compound of IN'4412 anywhere in D1. Second, the Applicant submits that by reading some lines from IN'4412 application so as to draw a comparison with D1 is false and read out of context. ***There is no similarity in D1 and IN'4412 as both D1 and IN'4412 relate to two separate inventions .***The test for patentability is to assess the novel and inventive concept of the application.

The applicant argued *that* there is no teaching, suggestion or motivation in WO'345 to arrive at compound of subject application 4412. The inventive compound is therefore not obvious for following reasons:

The applicant argued that **WO2003/059345 (WO '345)** has been relied by all the Opponents. WO '345 discloses a pharmaceutical composition comprising valsartan or a pharmaceutically acceptable salt thereof and sacubitril or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. With regard to the teaching of WO '345, the Applicant reiterates the submissions made in paras 42-46 referred to above under Ground I.

The applicant submitted that the specification of IN'4412 and WO'345 are clearly not identical, Applicant notes for completeness that even if the specifications of two patent applications are identical (which is clearly not the case here), it does not necessarily mean that the earlier application anticipates the later filed application.

The applicant relies on the refrence is placed on :

Lallubhai Chakubhai Jariwala Vs. Chimanlal Chunilal and Co. [AIR1936Bom99], at para 10 it was held that:

…the earlier publication must give the requisite knowledge clearly, and it is not enough that it merely gives the means ofttaining such knowledge. It must give sufficient information to a workman skilled in the particular art or craft in order to enable him to carry out the invention. How far that knowledge anticipates the new invention is again a question of fact depending on the facts and circumstances of each case. ***Even where the prior document and the present specification are identical or nearly identical in language, it does not necessarily follow that the Court must conclude that the first is an anticipation of the second****, and often expert evidence is necessary to help the Court to consider what knowledge the prior publication could have conveyed to the mind of a person who had not the knowledge given by the invention in dispute.*

The applicant argued that *the invention of the present application IN'4412 is different from that of WO'345. WO'345 relates to a combination of two actives namely Valsartan and Sacubitril whereas the present application, IN'4412 relate to a supramolecular compound (a single unique compound of the two said actives). The commercial product Entersto / Vymada of the Applicant is a result of research of the said two inventions namely WO'345 and IN'4412 applications.*

The applicant further argued that the subject matter of the compound patent differs from the WO '345 in at least the following respects.

a) **molar ratio is 1:1:** in the invention, valsartan and sacubitril are provided in the particular molar ratio of 1:1, i. whereas the ratios of valsartan and NEP inhibitor which may be administered are left open in WO '345 (see, for instance, WO '345, page 15, second para);

b) **administration together**: in the invention, valsartan and sacubitril are provided in a form that necessitates their administration together, i. whereas in WO '345 the physical relationship of the individual active substance's valsartan and sacubitril is left open (see, for instance, WO '345, page 13, second §); and

c) **Single Compound**: Valsartan and Sacubitril are constituents of a single defined compound – specifically a compound also including three sodium cations and 0-3 water molecules, i. whereas in WO'345 the chemical relationship between the individual active substances valsartan and sacubitril is left open.(***para 4.4 of Dr. Myerson's affidavit)***

The applicant argued that *there is no teaching in WO'345 towards dual-acting compound (unique novel compound) that combines two active ingredients with two different modes of action havinganintricatenetworkandstabilizedbyaninvolvednetworkofionic,hydrogenand coordinationbonds.*

Para 4.4 of Dr. Allan Myerson's affidavit.

> 4.4 There is no disclosure in D1 of the claimed unique compound comprising the two components (valsartan and sacubitril) in their respective anionic form together with sodium cations and water molecules, linked together with non-covalent bonds to form a single large and highly intricate supramolecular structure. There is also no teaching or suggestion in D1 towards combining valsartan and sacubitril into a single supramolecular compound, and no indication of how such a compound could be made.

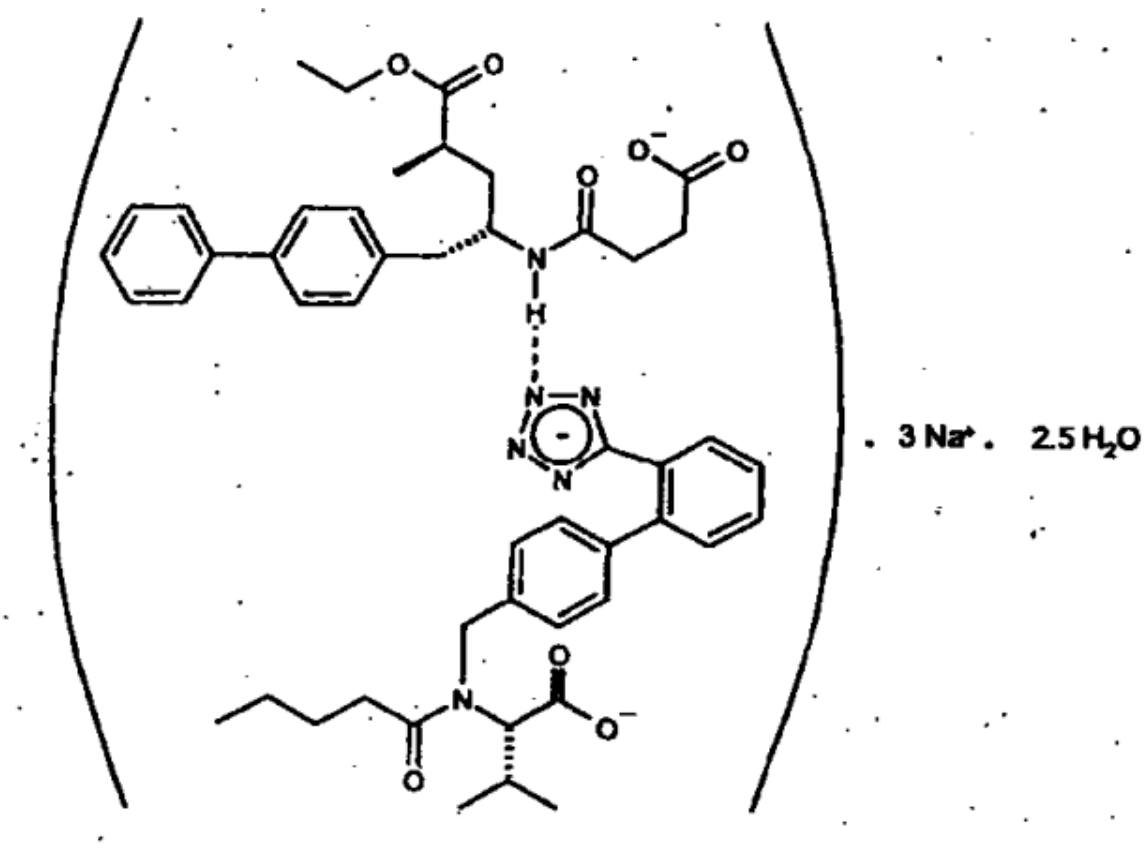
The applicant further submitted that, IN'4412 application relates to a **supramolecular compound** comprising two active ingredients/ moieties (a) an angiotensin receptor blocker (Valsartan), (b) neutral endopeptidase inhibitor (Sacubitril) and sodium cations in

a precise stoichiometric ratio, preferably 1:1:3. The compound may optionally further contain water molecules and has a hydration state defined in the claims by "x", which is 0-3 in claim 1, such as 0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 1, 2.25, 2.5, 2.75, or 3 (*p. 22 second to last paragraph and p. 23*). The compound is a **single entity** that is stabilized by non-covalent interactions (including hydrogen bonds, ionic bonds and van der Waals forces).

The preferred embodiment in the IN '4412 is wherein "x" is 2.5, i.e., a hemipentahydrate and *(p. 22, second to last paragraph, of the specification of the 4412 Application*) is specifically claimed by claims 2 and 3 of the present application. The said embodiment is trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate]-hemipentahydrate. This preferred embodiment is exemplified in Examples 1-3 of the IN '4412 Application *(pages 40-43 of the specification)* and is fully characterized by various analytical and spectroscopic techniques *(p. 24-29 and 43-45 of the specification).* The therapeutic effect of the claimed compound has been confirmed in the representative animal studies performed and described in the specification of the IN '4412 Application (*p. 33-35 and paras 2.1 to 2.11 of Dr. Myerson's affidavit).*

a) The single crystal X-ray diffraction (SCXRD) data for the exemplified embodiment of the claimed supramolecular compound reveal a highly unusual and intricate three-dimensional structure, as summarized on page 28 of the specification of the IN'4412 Application.

b) A simplified structure of the said embodiment is shown below *(p.23 of the specification):*



The unique structural feature of the preferred embodiment of the present invention: The aforementioned preferred embodiment is a representative compound of the claimed invention known as LCZ696. Crystalline LCZ696 (referred to herein as "LCZ696") is unique with a complex interaction of ionic and hydrogen bonding between Valsartan anions, Sacubitril anions, sodium cations and water. The asymmetric unit of the crystalline supramolecular complex consists of:

a) 6 molecules of Valsartan in its anionic form;

b) 6 molecules of Sacubitril in its anionic form;

c) 18 sodium cations;

d) 15 water molecules;

e) Monoclinic unit;

f) molecular formula of $C_{288}H_{330}N_{36}O_{48}Na_{18}\cdot 15H_2O$ (M.W. 5748.03);

g) The sodium cations are coordinated by oxygen ligands derived from **twelve carboxylate groups** and **eighteen carbonyl groups** (in the Sacubitril anions and Valsartan anions), and from 13 of the 15 water molecules (*see page 29, 3rd para of the patent specification* of IN'4412 application). The interactions are defined in the specification wherein the sodium cations are preferably coordinated to several oxygen ligands which come from carbonyl and carboxylate groups (*page 11, para 3 of the complete specification*).

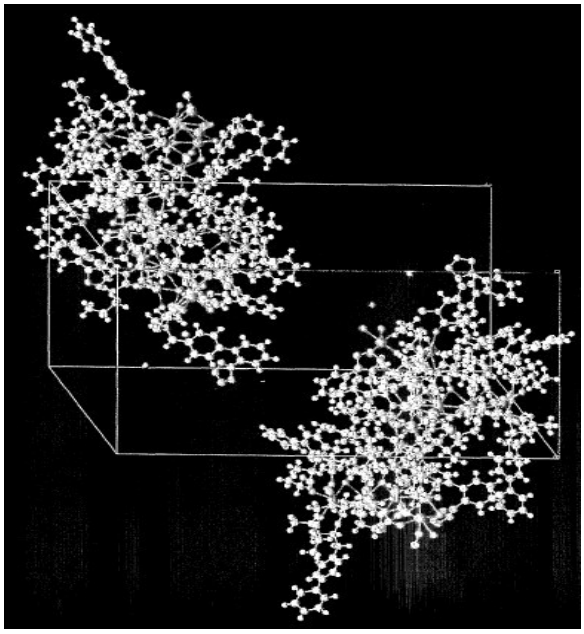
h) In all six of the Valsartan moieties, the tetrazole rings do not have an ionic bond directly to sodium, but instead form a hydrogen bond to the amide NH of the Sacubitril moieties; the amide carbonyl groups coordinate to the sodium ions. In addition, the tetrazole ring forms hydrogen bonds with water, which in turn forms part of the coordination polyhedra of the sodium ions. *(Feng et al., Fig.2).*

i) This **arrangement of sodium coordination is so efficient that each carbonyl and carboxy oxygen in both components is associated with multiple sodium ions**.

(Please refer to "interactions" as described in the specification and the Feng article submitted with affidavits of Dr. Allan S. Myerson & Dr. Michael Motto on June 6, 2020) as well as the patent specification of the IN'4412 Application@ page 24 and 29)

j) This interaction leads to an association that makes the compound distinct from a combination of ARB and NEPi obtained by simply physically mixing the two active agents. Thus, the compound has different physico-chemical properties that make it particularly useful for manufacturing and therapeutic applications (*pages 8, 11 and 24 last paragraph of the specification of the IN'4412 Application*).

k) The single crystal X-ray diffraction (SCXRD) data for the exemplified embodiment LCZ 696 of the claimed supramolecular compound reveal a highly unusual and intricate three-dimensional structure, *as summarized on page 28 of the specification of the 4412 Application.* A pictorial representation of the unit cell of the exemplified supramolecular compound, LCZ 696 comprising two asymmetric units is represented in *Fig. 1 of the IN 4412 Application*, and reproduced below:



Pictorial representation of the unit cell of LCZ696 *(page 29, paras 2-3 of the complete specification of the IN'4412 Application)*

l) The patent specification also illustrates the best method for performing the invention under Section 10(4) of the Indian Patents Act (*as examples 1-3*) by describing alternate methods for making the preferred embodiment.

m) Dr Allan Myerson's affidavit at paragraph 3.1 states that the claimed supramolecular compound reflects an **unusual approach for drug development** in particular of 2 actives in anionic form linked via cationic linking- it required an **OUT OF BOX THINKING.**

The applicant further submitted that any teaching suggestion or motivation, there is a clear teaching away from modifying WO 345 to arrive at the present invention as b) WO '345 allows for considerable flexibility in dosages and dosing regimens (p. 15), for example teaching that valsartan and sacubitril can be dosed at different dosing frequencies and that the amounts of valsartan and sacubitril can differ or be the same and is left open. c) The claimed compound of the present application removes the dosing flexibility option as provided by WO 345 as it dictates a fixed 1:1 molar ratio of valsartan and sacubitril, dosed together. This is a significant constraint on the final formulation making it less flexible to develop. The person skilled in the art would be reluctant to lose the dosing flexibility allowed in WO'345 and would not be motivated to consider the supramolecular compound approach.

The Applicant submitted that there is no teaching in WO '345 that would have prompted a person skilled in the art to arrive at the claimed supramolecular compound of Valsartan and Sacubitril.

Arguments and Submission by opponents and Applicant on D2 (US5217996)

ACTIVE INGREDIENTS PER SE AND IN SALT FORM OF THE CLAIMED COMPLEX KNOWN IN THE ART (PRIOR PUBLISHED APPLICATIONS MADE BY THE APPLICANT):

The opponent 2(Natco Pharma Ltd.) relied on the *D2 (US5217996) By Novartis Corp and submitted that* D2 discloses the specific NEPi inhibitor and the sodium salt thereof is exemplified. N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2Rmethylbutanoic acid ethyl ester and is specifically disclosed and Sodium N-(4-carboxy-1-oxobutyl)-(4S)-p-phenylphenylmethyl-4-amino-2Rmethylbutanoic acid ethyl ester, melting at 68°-72° C are specifically exemplified and disclosed. *(Column 21 lines 66 to 68 and column 22 example 4)*

The compounds, including their salts, may also be obtained in the form of their hydrates, or include other solvent used for the crystallization. (Column 16 lines 2 to 5)

The compounds of the invention are thus particularly useful for the treatment of conditions and disorders responsive to the inhibition of neutral endopeptidase EC 3.4. 24.11, particularly cardiovascular disorders, such as hypertension, renal insufficiency including edema and salt retention, pulmonary edema and congestive heart failure. (Column 1, Summary of the Invention)

The opponent 2(Natco Pharma Ltd.) **submitted that** THEREFORE, D2 TEACHES

- **Sacubitril and the sodium salt thereof for the treatment of congestive heart failure.**

The opponent 3 &6 (Kumar Sushobhan & G. Sriniwas Rao) submitted US996 discloses NEP inhibitors including Sacubitril, N-(3-carboxy-1- oxopropyl)-4-(p-phenylphenylmethyl)-4-amino-2-methylbutanoic acid ethyl ester. **The only salt form exemplified for the NEP inhibitors discloses therein including Sacubitril is the sodium salt form** [Please refer Examples 3 to 6].

US 996 discloses in lines 56 to 59 in column 15 that *"**any resulting free acid** or base **can be convertedinto a corresponding metal**, ammonium or acid addition **salt** respectively, **by reacting it with an equivalent amount of the corresponding base**……"* In line 63 to 65 in same paragraph it is stated that *"Any resulting salt may also be converted into the free compound, by liberating the latter with stronger acids or bases, respectively."*

Above disclosure teaches a person skilled in the art that Sacubitril which is one of the NEP inhibitors disclosed can be converted into its metal salt such sodium salt by reacting it with equivalent amount of corresponding base i.e. if sodium sacubitril has to be prepared it should be reacted with NaOH in equivalent amounts. The process of the impugned application also discloses reaction of the free acid i.e. the APIs sacubitril and valsartan to be reacted with corresponding base i.e. NaOH (sodium hydroxide) in order to form sodium salt.

The aforementioned disclosure also teaches PSITA that thus formed metal salt of the API when subjected to strong acid will again break into its corresponding original API. Therefore, PSITA is taught that if the said sodium salt of Sacubitril is used it will dissociate into sacubitril once it reaches the highly acidic environment of human stomach and the API will be free to act on its target site.

Further, in column 16 in lines 3 to 5 it is stated that "***The compounds, including their salts, may also be obtained in the form of their hydrates**, or include other solvent used for the crystallization.*"

Lines 47 to 52 in column 9 disclose that "The antihypertensive activity can be determined in the **spontaneously hypertensive rat (SHR)**, Goldblatt rat or Goldblatt dog by direct

measurement of blood pressure. Advantageously, the effect is measured in **the DOCA-salt hypertensive rat** and/or renal hypertensive rat or dog model."

Lines 7 to 9, and 11-12 in column 11 state that "N-(3-carboxy-1-oxopropyl)- (4S)-(p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester [i.e. **Sacubitril]** …….. **produces significant increases in plasma ANF levels**."

It is stated in Lines 13 to 15 in column 11 that "**The antihypertensive effect can be determined in** desoxycorticosterone acetate **(DOCA)-salt hypertensive rats**." And in lines 32 to 37 it is stated that "N-(3-carboxy-1-oxopropyl)-(4S)- (p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester **[i.e. Sacubitril]**…….. **produces a significant reduction in blood pressure in the DOCA-salt hypertensive rat model**."

It is disclosed in line 59 to 61 in column 18 of US996 that "**A unit dosage for a mammal of about 50 to 70 kg may contain between about 10 and 100 mg of the active ingredient**." It is noteworthy that a 70 kg is considered by people in the field to be the average weight of an adult male. Therefore, 70kg mammal as described in US996 includes an adult human being.

It is pertinent to note that the animal models used to study the effect of Sacubitril are same as that used in WO345 i.e. DOCA hypertensive rat model and SHR model and US996 also discloses dosage to be used in a mammal i.e. human being. The data disclosed in US996 clearly establishes that Sacubitril was effective in reducing hypertension and increasing levels of beneficial peptides i.e. ANFs.

The opponent 3 &6 (Kumar Sushobhan & G. Sriniwas Rao) submitted that the applicant has stated that since Sacubitril was not approved bya regulatory authority on date of impugned invention PSITA has no motive to use Sacubitril, let alone combine it with Valsartan. However, as seen from the disclosure of WO345 and US996, the therapeutic effect of Sacubitril in hypertension and related diseases was well established and the people in the field taught a combination of Valsartan and Sacubitril to be even more effective than using Valsartan alone or Sacubitril alone.

The opponent no 4 (Dr. Reddy's Laboratories Ltd.) submitted that the prior art document D2 Research Article titled as "Hydrogen-bond directed co-crystallization as a tool for designing acentric organic solids" by Etter et al. teaches a process for preparing a 1:1 co-crystalline complex of 4-aminobenzoic acid (4- ABA) and 3,5-dinitrobenzoic acid (3,5-DNBA) via a hydrogen bonding.

The opponent no 4 (Dr. Reddy's Laboratories Ltd.) further submitted that the **document D2** teaches co-crystallization of organic compounds. It is submitted that D2 teaches two methods of production of same co-crystal of two anions: (i) solution co- crystallization, and (ii) solid-

state grinding, in as early as 1988, when the article was published. It is submitted, hence, that the methods of co-crystallization of the organic compounds are well known in the art and in fact common general knowledge for a practitioner in the field.

The opponent no 4 (Dr. Reddy's Laboratories Ltd.) submitted that the claimed compound is a combination of valsartan and sacubitril having 3 moles of sodium 2.5 moles of water in the form of a complex, towards which, ample teaching and suggestion exists in the art.

The opponent no 4 (Dr. Reddy's Laboratories Ltd.) submitted that a complex formation of two anionic moieties ar

known in the art for a long time, especially between two anionic moieties as already disclosed in D2. ***(Reference: page 75 of Annexures, column 2, para 3, 4 and 5 con to para 1 on page 76) (Reference: page 76 of Annexures, column 1, para 2)***

The opponent no 4 (Dr. Reddy's Laboratories Ltd.) submitted a person having ordinary skill in the art will be motivated to form complex with valsartan and sacubitril since both are anions and combination of these two agents have better therapeutic profile than the individual components in light of the combined teachings of D1.

The opponent no 4 (Dr. Reddy's Laboratories Ltd.) submitted that impugned application has no advantages/ technical advancement over the over the combination, as taught in D1, as elaborated herein below:

(i) One of the advantages as claimed by the Applicant is a fixed 1:1 molar ratio of sacubitril and valsartan. D1 covers a pharmaceutical composition comprising valsartan and Sacubitril in 1:1 ratio. Therefore, the fixed 1:1 dose ratio of valsartan and sacubitril is already known and achieved in the prior art and hence does not provide any advantageous property of the complex.

(ii) Second advantage as claimed by the Applicant is the simplification in compounding and manufacturing of drug product. It is submitted that many combination products have been approved and are being manufactured routinely. Hence, this should not be treated as an advantage/ technical advancement over what is already known in the art. Further, it is submitted that the applicant has exemplified in the examples of D1 the method of manufacture of a drug product which is a combination of Sacubitril and Valsartan. It is therefore submitted that a person having ordinary skill in the art would know how to prepare a drug product which is a combination of Sacubitril and Valsartan from D1.

(iii)The third advantage, as per the applicant is better physical properties of the complex like less hygroscopicity and better solubility. It is submitted that the applicant is trying to imply that valsartan is so hygroscopic that it is not easy to formulate valsartan into a drug product. However, valsartan tablet is available in India since long and many companies in India have been manufacturing valsartan tablet for a long period. It is submitted that the applicant has only mentioned that the complex has better solubility but does not provide any data to further its claim. Hence, the advantage regarding solubility is also questionable herein by because of lack of data/evidence.

(iv)**The opponent no 4 (Dr. Reddy's Laboratories Ltd.) submitted** that the complex of the impugned application is obvious over the combination of valsartan and sacubitril as disclosed in D1 and there is no advantage of the complex over the combination. It is submitted that due to lack of any advantage of the complex over the combination, as known in D1, the complex lacks inventive step.

The opponent no 4 (Dr. Reddy's Laboratories Ltd.) submitted that the patent applicant has submitted Izzo et al. (J Cardiovascular Pharmacology; Vol. 69 No. 6, June 2017; Annexure – B) to show that claimed co-crystal of sacubitril and valsartan have enhanced therapeutic efficacy ***(Reference: Para 40(c) of Patent Applicant reply, Pg 43)*** over existing knowledge. Specifically, patent applicant argued that LCZ696 (400mg) have 37% less percentage of valsartan over a combination of Valsartan (320 mg) and Sacubitril (200 mg) but have similar efficacy. It is submitted that patent applicant analysis of Izzo et al. is misleading and should be

rejected in toto. Izzo et al., ***(Reference: page 379, Figure 4)*** discloses proportion of patients achieving BP control at end point for different combination of Sacubitril and valsartan. The following table relates the proportion of patients SBP and BP control for important combinations and LCZ696:

Drug	Proportion of patients achieving BP control	Proportion of patients achieving SBP control
Sacubitril + Valsartan (100mg +320 mg)	50.4*	56.7*
LCZ696 400 mg [Sacubitril (194 mg) + Valsartan (206 mg)]	53.5*‡	57*
Sacubitril + Valsartan (200mg +320 mg)	59.7*‡	65.3 *‡

The opponent no 4 (Dr. Reddy's Laboratories Ltd.) submitted that in view of above table it is aptly clear that LCZ696 400 mg have similar effectiveness for SBP control (57*% vs 56.7%*) as compare to a combination Sacubitril (100 mg) + Valsartan (320 mg), though it has almost 50% of Sacubitril as of LCZ696 400mg. Further, Izzo et al., ***(Reference: Figure 2)*** shows reductions in office (A) and ambulatory (B) BP and PP at end point. The following table relates reductions in office (A) and ambulatory (B) BP and PP for important combinations and LCZ696:

Drug	Reductions in office (A)-SBP	Reductions in office (A)-PP	Reductions in ambulatory (B)-SBP	Reductions in ambulatory (B)-PP
Sacubitril + Valsartan (100mg +320 mg)	-21.3*§	-13.2*§	-14.3 *‡	-7.7 *‡
LCZ696 400 mg [Sacubitril (194 mg) + Valsartan (206 mg)]	-21.8*§	-12.2*§	-13.0 *§ll	-6.8 ‡l

Sacubitril + Valsartan (200mg +320 mg)	-23.6 *‡	-13.9 *‡	-15.7*‡	-8.5*‡

The opponent no 4 (Dr. Reddy's Laboratories Ltd.) submitted above table it is aptly clear that LCZ696 400 mg have similar effectiveness for SBP and PP control as compare to a combination Sacubitril (100 mg) + Valsartan (320 mg), though it has almost 50% of Sacubitril as of LCZ696 400mg. Further, Izzo et al, ***(Reference: page 378)*** admitted that reduction in SBP and PP with the free combination of Sacubitril 200 mg + valsartan 320 mg were slightly greater than those with LCZ696: *"Reductions in 24-hour ambulatory SBP and PP with the free combination of sacubitril 200 mg+ valsartan 320 mg [215.7 (0.7) an 28.5 (0.4) mm Hg, respectively] were slightly* ***greater*** *than those with LCZ696400 mg [213.0 (0.7) and 26.8 (0.4) mm Hg, respectiv99ely, P, 0.05]."*

The opponent no 4 (Dr. Reddy's Laboratories Ltd.) submitted *that* Importantly, Izzo et al. ***(Refence: last page 380 under discussion section)*** does not conclude that is LCZ696 has similar efficacy to the combination of free valsartan 320 mg plus free sacubitril 200 mg. Instead, it says *"Results of this study also showed a similar safety and tolerability profile of LCZ696 to valsartan and all of the coadministered free combinations of Sacubitril and valsartan"*

The opponent no 4 (Dr. Reddy's Laboratories Ltd.) submitted that Claim 6 of the impugned application covers a process for preparation of the claimed complex which comprises dissolving valsartan or salt thereof and sacubitril or salt thereof in a suitable solvent; dissolving basic sodium in a suitable solvent; combining both the solutions and precipitation and drying the resulting complex.

The opponent no 4 (Dr. Reddy's Laboratories Ltd.) submitted that D2 provides important roadmap to the production of supramolecular structure. It motivates and teaches a person skilled in art to develop a supramolecular form of pharmaceutical compound disclosed in D1. It is submitted that D2 provides sufficient motivation to develop a supramolecular complex.

The opponent no 4 (Dr. Reddy's Laboratories Ltd.) submitted that the process for synthesizing the complex is so general and vague that as per the Claims of the impugned application it takes place without any exact reaction conditions and it takes place in any solvent, in presence of any sodium base or starting material and at any temperature and pressure. It is submitted that in view of the fact that the process of synthesizing the complex becomes obvious over D2 inasmuch as no clear and unambiguous advantage of the claimed process over the known process for synthesizing a complex is shown by the Applicant. Moreover, a person skilled in the art

reading the claims and specification of the impugned patent would be unable to follow the invention without undue experimentation.

The opponent no 4 (Dr. Reddy's Laboratories Ltd.) submitted that the present application is liable to rejected on basis of lack of inventive step over combined teachings of D1 and D2. Claim 6 is related to a process for the preparation of a complex of Sacubitril and valsartan. It is respectfully submitted that the impugned specification discloses various "aspect of impugned invention" ***(Reference: Page 5, 7 and 8 of the complete specification of the present application)*** for preparing dual acting compounds from ARBs and NEPi. According to the impugned specification, the process is applicable to various ARBs and NEPi, irrespective the nature of compounds. Further, the specification is silent about any technical effect of the claimed process. Essentially, the patent applicant is trying to claim a general process which is well recognized in the art.

The opponent no 4 (Dr. Reddy's Laboratories Ltd.) submitted that the patent applicant in his ***(Reference: paragraph 32 at page 34)*** specifically denied that the process of LCZ696 is not a solution co-crystallization. Specifically, claim 6, step (a) involves the preparation of solution of Sacubitril and valsartan. Therefore, claim 6 process covers a process which involve solution co-crystallization (specifically taught by D2). Thus claims 6-8 lack inventive steps.

Applicant Arguments and Submission(NOVARTIS AG.) on D2 (US5217996)

The applicant submitted that D2, US5217996 (US '996) discloses neutral endopeptidase inhibitors, in particular "Sacubitril and its sodium salt. Example 8 of US '996 discloses preparation of sodium salt of Sacubitril capsules containing 50 mg of [N-(3-Carboxy-1-oxopropyl)-(4S)-p-phenyl phenyl methyl)-4-amino-2R-methyl butanoic acid, ethyl ester]. However, it is irrelevant that US '996 discloses a sodium salt of Sacubitril because US 996 does not disclose any combination of Sacubitril (or a sodium salt of Sacubitril) with Valsartan. US'996 therefore provides no relevant teaching towards the invention. The IN'4412 application makes reference to US '996 in their patent specification.

The applicant submitted that POSA will become aware that sodium salt of Sacubitril is not good for further development as the said salt of Sacubitril is hygroscopic as shown below.

PROPERTY	*LCZ696*	*VALSARTAN DISODIUM SALT*	*SACUBITRIL MONOSODIUM SALT*
Hydration	2.5 H_2O	3 H_2O	anhydrous
Hygroscopicity (% at 60% relative humidity)	0.6	5	13
Hygroscopicity (% at 75% relative humidity)	6.9	6.5	26

The applicant argued that the amount of absorbed moisture in a drug can influence the **flow and compression characteristics of powders** during manufacture and can have an

impact on the hardness of final tablets and granulations. Water absorption by Active Pharmaceutical Ingredients (APIs) also frequently **affects the physical and/or chemical stability of final dosage** forms and always introduces serious content uniformity concerns. ***This again will not motivate person skilled in the art (POSA) to use monosodium salt of Sacubitril and there is a clear teaching away.***

Opponent Arguments and Submission on D3 (W02/06253)

The opponent 2,3&4,6 relied on the prior art Document *D3 (W02/06253) By Novartis AG*
D3 discloses about valsartan and the mono-sodium and disodium salt and hydrate There of (Example 5, 10 and page 3)

The opponent 2 (Natco Pharma Ltd.) submitted that *the active ingredient valsartan is the free acid which is described specifically in EP 0443983, especially in example 16; it has two acidic hydrogen atoms: (i) the hydrogen atom (H atom) of the carboxyl group, and (ii) that of the tetrazole ring. Accordingly, one acidic H atom (primarily the carboxyl H atom) or both acidic H atoms may be replaced by a monovalent or higher valent, e.g. divalent, cation. Mixed salts may also be formed. (page 1)*

Preferred salts are for example selected from the mono-sodium salt in amorphous form; di-sodium salt of valsartan in amorphous or crystalline form, especially in hydrate form, thereof. (Page 3)
Compared with the free acid, the salts according to the invention, or the amorphous forms, solvates such as salt hydrates, and also the corresponding polymorphous forms thereof, have unexpectedly advantageous properties. (Paragraph bridging pages 3 and 4).
The description salt hydrates for corresponding hydrates may be preferred, as water molecules in the crystal structure are bound by strong intermolecular forces and thereby represent an essential element of structure formation of these crystals which, in part, are extraordinarily stable. However, water molecules are also existing in certain crystal lattices which are bound by rather weak intermolecular
forces. Such molecules are more or less integrated in the crystal structure forming, but to a lower energetic effect. The water content in amorphous solids can, in general, be clearly determined, as in crystalline hydrates, but is heavily dependent on the drying and ambient conditions. In contrast, in the case of stable hydrates, there are clear stoichiometric ratios between the pharmaceutical active substance and the water. In many cases these ratios do not fulfil completely the stoichiometric value, normally it is approached by lower values compared to theory because of certain crystal defects. The ratio of organic molecules to water molecules for the weaker bound water may vary to a considerable extend, for
example, extending over di-, tri- or tetra-hydrates. ….. (Paragraph bridging pages 5 and 6) *That the salts or combinations according to the present invention can be used for the treatment of renal failure, especially chronic renal failure, can be demonstrated using the test model described, e.g., by D. Cohen et al. in Journal of Cardiovascular Pharmacology, 32: 87-95 (1998).*

The opponent 2 (Natco Pharma Ltd.) **submitted** *that* THEREFORE, **D3** TEACHES **Valsartan and its salts by itself and in combination with NEPi for the treatment of congestive heart failure.**

The opponent 2 (Natco Pharma Ltd.) submitted that " it is clear from D1 to D3 that the active ingredients, namely, Valsartan and Sacubitril were known at the date of the present invention. Most significantly, the combination of the two actives was also known to have unexpected therapeutic efficacy."

The opponent 2 (Natco Pharma Ltd.) **submitted submitted** that the invention relates to new salts of valsartan or crystalline. The object of the invention stated in second paragraph on page 2 is *"**There is a need for more stable, e.g. crystalline forms of valsartan,which are even easier to managein the drying or grinding** processes following the final stage of the chemical preparation process **and also in the steps for preparing the pharmaceutical formulations**."*

The opponent 2 (Natco Pharma Ltd.) **submitted that** Page 3 of the document discloses preferred salt forms wherein it is stated that *"**Preferred salts** are for example selected from …….**di-sodium salt of valsartan** in amorphous or **crystalline form, especially in hydrate form**, thereof."*

It is disclosed in bridging paragraph of page 3 and page 4 that *"**Compared with the free acid**, the salts according to the invention, or the amorphous forms, **solvates such as salt hydrates, and also the corresponding polymorphous forms thereof, have unexpectedly advantageous properties**. Under given conditions, the crystalline salts and **crystalline salt hydrates have a clear melting point which is linked with a marked, endothermic melting enthalpy**. The **crystalline salts** according to the invention are **stable and are of better quality than valsartan also during storage and distribution**. The amorphous or partially amorphous salts have limited stability, i.e. as the solid, they have a restricted stability range. To be stabilised, they require certain measures which can be achieved for example by galenic formulations."*

The opponent 2 (Natco Pharma Ltd.) **submitted that second paragraph on page 4 discloses** that *"In addition, both the **crystalline** and the amorphous **salts** according to the invention have **a high degree of dissociation in water and thus substantially improved water solubility**. These properties are of **advantage**, since on the one hand **the dissolving process is quicker** and on the other hand a smaller amount of water is required for such solutions. Furthermore, the **higher water solubility** can, under certain conditions, also lead to **increased biological availability of the salts or salt hydrates in the case of solid dosage forms**. **Improved properties are beneficial especially to the patients**……For different relative humidities at room temperature and also at a slightly higher temperatures, **the salt hydrates** according to the invention **show practically no water absorption or water loss over a wide range of humidities and for periods of a few hours**, e.g. four hours. Also, for example, the **melting point of the salts** according to the invention **will not be changed by storing under different relative humidities**."*

The opponent 2 (Natco Pharma Ltd.) **submitted submitted that WO253 teaches** a PSITA that the crystalline salt forms, especially crystalline salt hydrates of Valsartan have numerous advantages over Valsartan free acid which includes better water solubility, higher stability, higher bioavailability, no

water absorption or water loss on keeping (i.e. much less or no hygroscopicity), betterstability. Therefore, a PSITA is taught to use Valsartan crystalline salt hydrate form over Valsartan free acid.

Further, the Applicant in their reply statement has stated that the compound of impugned application possesses the advantage of higher solubility, less hygroscopicity, higher stability, better stability. However, it's evident from the aforementioned disclosure that such properties were inherent and already known in art in the Valsartan salt crystalline hydrate such as crystalline disodium hydrate of Valsartan, which is exemplified in WO253.

Furthermore, since the preferred salt of Sacubitril is sodium salt, as taught in WO345 and US996, and since WO345 teaches to combine Valsartan and Sacubitril a PSITA will inevitably choose to have sodium salt of Valsartan, too in the combination since use of same salt form has lower propensity for incompatibilities between the APIs rather than using different salt form for each of the API. In view of teaching of WO253 the PSITA is bound to have crystalline disodium salt of Valsartan which is in hydrate form.

Third paragraph on page 5 discloses that *"Solvates and also **hydrates of the salts** according to the invention may be present, for example, as **hemi-, mono-, di-, tri-, tetra-, penta-, hexa**-solvates or **hydrates**, respectively."*

Last paragraph on page 5 discloses that *"The description **salt hydrates** for corresponding hydrates may be preferred, as **water molecules in the crystal structure are bound by strong intermolecular forces and thereby represent an essential element of structure formation of these crystals** which, in part, are **extraordinarily stable**."*

WO253 discloses in last paragraph on page 5 that the **hydrate can hemi-, mono-, di-, tri-, tetra-, penta-, hexa-hydrate and that this water in the hydrate form is strongly bound in the integral structure of the crystal by intermolecular forces i.e. by non-covalent bonds.**

PSITA skilled in the art knows that in salt form counter-ions are bound by non- covalent bonds i.e. by ionic bonds and WO253 discloses that in hydrate salt form the water molecules are also bound by non-covalent bonds i.e. by string intermolecular bonds. The Applicant has portrayed in their reply statement that the claimed compound is unique because in said compound the interaction between the different components of compound is by non-covalent bonding. However, from above disclosure and from general understanding of a PSITA, it is evident that presence of different components of a compound with string non- covalent bonding with each other is nothing unique.

For the process of preparation of the salt, bridging paragraph of page 23 and 24 discloses that *"To form the salt, the process is carried out in a solvent system, in which the two reactants, namely the acid valsartan and the respective base, are sufficiently soluble. It is expedient to use a solvent or solvent mixture, in which the resulting salt is only slightly soluble or not soluble at all, in order to achieve crystallisation or precipitation. One variant for the salt according to the invention would be to use a solvent in which this salt is very soluble, and to subsequently add an anti-solvent to this solution, that is a solvent in which the resulting salt has only poor solubility. A further variant for salt crystallisation consists in concentrating the salt solution, for example by heating, if necessary*

under reduced pressure, or by slowly evaporating the solvent, e.g. at room temperature, or by seeding with the addition of seeding crystals, or by setting up water activity required for hydrate formation."

. Para 5 on page 24 outlines that process of preparation in further detail in which it is disclosed that

"The dissolving and crystallising process is characterised in that –

(i) ***valsartan and the appropriate base are brought to a reaction in a preferably water-containing, organic solvent,***

(ii) the solvent system is concentrated, for example by heating, if necessary, under reduced pressure and by seeding with seeding crystals or by slowly evaporating, e.g. at room temperature, then crystallisation or precipitation is initiated and (iii) the salt obtained is isolated."

Last paragraph on page 24 gives further process details and discloses that *"The equilibrating crystallisation process for producing hydrates is characterised in that (i) valsartan and the appropriate base are added to a water-containing organic solvent, (ii) the solvent is concentrated, for example by heating, if necessary under reduced pressure or by slowly evaporating, e.g. at room*

temperature, (iii) the residue of evaporation is equilibrated with the required amount of water by –

(a) suspending the residue of evaporation, which is advantageously still warm, and which still contains some water, in an appropriate solvent or

(b) by equilibrating the water excess in the solvent; whereby in a) and b) the existing or added water is present in a quantity in which the water dissolves in the organic solvent and does not form an additional phase; and (iv) the salt obtained is isolated."

. Para 5 on page 25 discloses that *"The equilibrating crystallisation process for producing hydrates is characterised in that (i) valsartan and the appropriate base are added to a water-containing organic solvent, (ii) the solvent is concentrated, for example by heating, if necessary under reduced pressure or by slowly evaporating, e.g. at room temperature, (iii) the residue of evaporation is equilibrated with the required amount of water by (a) suspending the residue ofevaporation, which is advantageously still warm, and which still contains some water, in an appropriate solvent or(b) by equilibrating the water excess in the solvent; whereby in a) and b) the existing or added water is present in a quantity in which the water dissolves in the organic solvent and does not form an additional phase; and (iv) the salt obtained is isolated……..…..****By using the dissolving and crystallising process, or the water-equilibrating crystallisation process, the defined hydrates, which are present in crystalline and in polymorphous forms, may be obtained reproducibly."***

. Furthermore, third paragraph on page 26 discloses that *"****These salts or salt hydrates according to the invention are obtained for example by neutralising the acid valsartan with a base corresponding to the respective cation. This neutralisation is suitably effected in an aqueous medium, e.g. in water or a mixture of water and a solvent in which valsartan is more soluble than in water."***

From the above disclosure of WO253 it is evident that the process of preparation of both the Sacubitril sodium salt and Valsartan sodium salt form are same i.e. both the processes require the free acid i.e. the API to be dissolved in a solvent and then reacted with corresponding base i.e. react with NaOH, sodium hydroxide, if sodium salt is to be prepared.

Furthermore, the detailed process outlined above as disclosed in WO253 has uncanny similarity to the process disclosed in the examples of the impugned patent application. Even the solvents used in the impugned application are same as those disclosed in WO253 on page 24 and 25 e.g. isopropyl alcohol, acetone, water etc.

. Importantly, **WO235** discloses that by applying the process disclosed therein the hydrates can be prepared reproducibly and in precise stoichiometery.

Third paragraph on page 33 discloses that *"**The invention similarly relates to combinations,** e.g. pharmaceutical combinations, **containing a** salt of the present invention or in each case a **pharmaceutically acceptable salt** thereof **in combination** with at least **one composition** for the treatment of cardiovascular diseases and related conditions and diseases as listed hereinbefore or hereinafter, **or in each case a pharmaceutically acceptable salt thereof**. "*

. Fourth paragraph on page 33 discloses that *"The **combination may be made for example with** the following compositions, selected from the group consisting of a:…….. (vi) dual angiotensin converting enzyme/**neutral endopeptidase** (ACE/**NEP) inhibitor or a pharmaceutically acceptable salt thereof**,"*

. Last paragraph on page 37 states that *"The **corresponding active ingredientsor a pharmaceutically acceptable salts thereof** may also be **used in form of** a solvate, such as a **hydrate** or including other solvents, used for crystallization."*

WO253 discloses that the salt forms of Valsartan disclosed therein can be used to form a combination with other active ingredients such as NEP inhibitors and that both the APIs in the combination can be salt form hydrate.

First paragraph on page 38 states that *"**The compounds to be combined can be present as pharmaceutically acceptable salts.If these compounds have,** for example, at least one basic center, they can form acid addition salts. Corresponding acid addition salts can also be formed having, if desired, an additionally present basic center. The compounds having **an acid group (for example COOH) can also form salts with bases.**"*

The above disclosure of **WO253** reveals that if the two APIs to be combined have acid group, they will form salt with bases. It is noteworthy that both Valsartan and Sacubitril have acid groups. Therefore, as per the teaching of **WO253**, both the APIs will form salts with bases in the combination. The same teaching is imparted by **WO345** document, too. Further, since WO345

and **US996** teaches to use Sodium salt of Sacubitril, it is obvious for the other component of the combination i.e. Valsartan to be used in sodium salt form, too.

In the preferred salts disclosed **in WO253,** it is disclosed that disodium salt of Valsartan is crystalline hydrate while sodium salt of Valsartan is amorphous. WO253 also discloses many advantages of crystalline hydrate salt forms over amorphous salt form. Therefore, PSITA is motivated to form disodium hydrate salt form of Valsartan as per WO253.

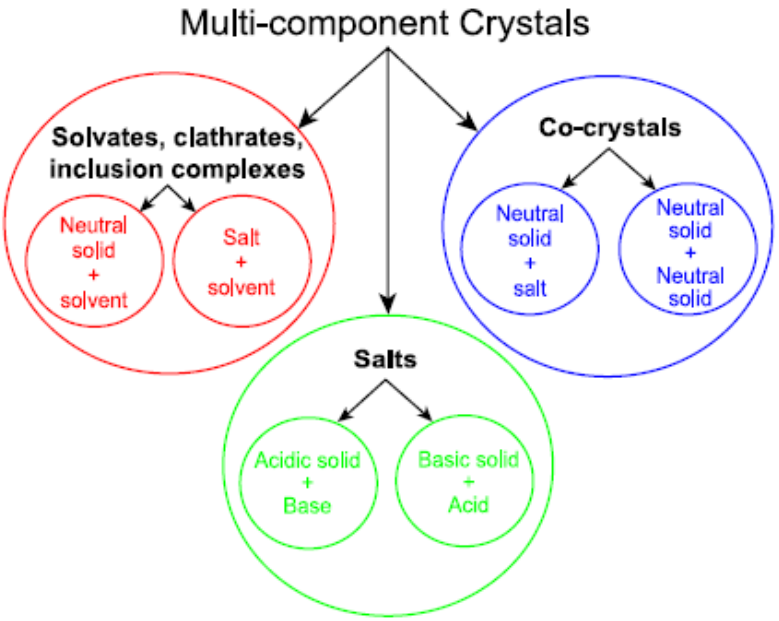
Example 5 on page 47 discloses **disodium salt of Valsartan** which is hygroscope and has high water content of 16%. However, when the same disodium salt is hydrated to get the hydrated product as exemplified in Example 11 discloses hemihydrate disodium salt of Valsartan (Valsartan**.**2Na**.**2.4 $\pm$ 1.0 mole H_2O) which is merely **slightly hygroscopic** and has a water content comparable to the water content other salt forms.

Above disclosure of WO253 reveals that while the disodium salt form of Valsartan is hygroscopic, the hydrate form of disodium Valsartan is merely slightly hygroscopic and has water content which is comparable to water content of calcium and magnesium salts. The precise stoichiometery of the number of moles of water to be present in this hydrate form has also been revealed by WO253 to be 2.4 $\pm$ 1.0.

Therefore, PSITA is motivated to choose Valsartan disodium hydrate (Valsartan**.**2Na**.**2.4 $\pm$ 1.0 mole H_2O) to be the preferred form of Valsartan.Furthermore, as per teachings of WO345 and WO253, it is obvious for a PSITA to combine Sacubitril and Valsartan, react with corresponding common base i.e. sodium hydroxide, NaOH by the detailed process outlined in WO253 to get the crystalline compound **Valsartan.Sacubitril.3Na. 2.4 $\pm$ 1.0 H_2O**, which is the subject matter of impugned application.

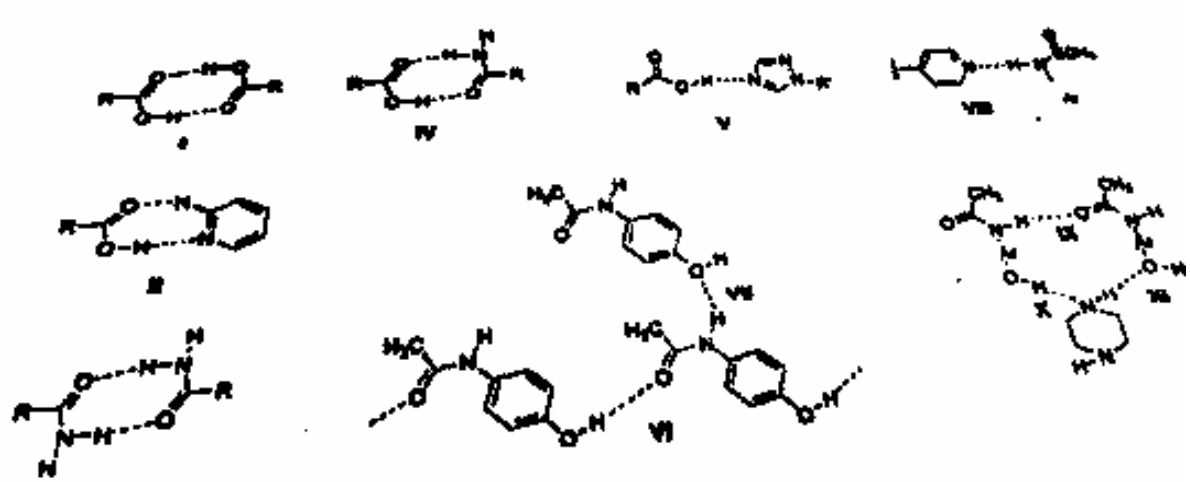
The opponent (Kumar Sushobhan & G. Sriniwas Rao) 3 and 6 submitted that the Applicant did not invent any supramolecular complex or co-crystal, the same was already known in the art. Many skilled workers have prepared several molecules and complexes of various compounds. The publication Morisette et al, 2004 (page 203 of the opposition) teaches that APIs can exist in a variety of distinct and solid forms including hydrates and co-crystals. (page 276, column 1, para 1) The relevant portion reads as under:

"Active pharmaceutical ingredients (APIs) are frequently delivered to the patient in the solid-state as part of an approved dosage form (e.g., tablets, capsules, etc.). Solids provide a convenient, compact and generally stable format to store an API or a drug product. Understanding and controlling the solid-state chemistry of APIs, both as pure drug substances and in formulated products, is therefore and important aspect of the drug development process. APIs can exist in a variety of distinct solid forms, including polymorphs, solvates, hydrates, salts, co-crystals and amorphous solids, ..." "... Morrisette et al further teaches types of co-crystals include Neutral sold + salt and neutral solid + neutral solid [pg. 293; Scheme 2]



Scheme 2. Types of multicomponent crystals.

"... It also teaches that the supramolecular synthons in synthesizing co-



crystal containing pharmaceutical agent and further states that supramolecular synthons observed in co-crystals include hydrogen bonding between moieties [Page 294, Scheme 3]

III Scheme 3: Supramolecularsynthons observed in co-crystals

The opponent (Kumar Sushobhan & G. Sriniwas Rao) 3 and 6 submitted therefore, combining two different molecules such as two different APIs by a common process to form a co-crystal was a concept which was well known in art at the time of the impugned invention. Thus, PSITA who was being taught to by WO345 and WO253 to combine to different molecules i.e. Valsartan and Sacubitril, and reacting them with corresponding common base to form salt hydrate crystalline form was not being presented by an hitherto unknown idea.

The concept of combining two different molecules to form co-crystal was already known and in light of this knowledge it was merely routine for PSITA to follow the teachings of WO345 and /or

WO253 to form co-crystal of Valsartan and Sacubitril in which Valsartan and Sacubitril were present as the neutral salt hydrate form.

The opponent (Kumar Sushobhan & G. Sriniwas Rao) 3 and 6 submitted that the Applicant has contended that **Morissett**e calls for forming co-crystals using different neutral molecules while Valsartan and Sacubitril are charges molecules. The Applicant's contention is against the fundamental natural principals of chemistry since any material that exists in solid state is in neutral state regardless of whether the individual constituent molecules of this solid may have the potential to acquire a charge in solution phase. Therefore, the process of preparation of salt hydrate form disclosed in US996 and WO253 which requires the molecules of Valsartan and Sacubitril in solvent and then reacting these with a corresponding base falls within the scheme taught in Morissette et al since Valsartan and Sacubitril are both neutral solids which can be combined as per teachings of **WO345 and WO253 to** form a co-crystal. The paper published by **Christer B.,** 2005 discloses that supramolecular complex may be prepared by bringing two separate distinct compounds together. The relevant portion is extracted herein below for ready reference:

"...co-crystallization is a deliberate attempt at bringing together different molecular species within one periodic crystallinelattice without making or breaking covalent bonds. Recrystallization and co-crystallization processes are, in essence, only distinguishable by their intents. The goal of the former is ahomomeric product, whereas the latter forms a heteromeric product."..

...co-crystallization compounds constructed from discrete neutral molecular species are considered as co-crystals. A co-crystal is a structurally homogeneous crystalline material that contains two or more neutral building blocks that are present in definite stoichiometric amounts…."

Further, both Morissette and Christer teach that a co-former forms non-covalent bonds with the different molecules and gets incorporated via non-covalent bonds into the co-crystal as an integral part of the co-crystal. It is submitted that the sodium molecules and water molecules of the salt hydrate act as co-formers which form non-covalent bonds with Valsartan & Sacubitril and gets incorporated via non-covalent bonds into the co-crystal as an integral part of the co-crystal. From the teachings above, it is clear that when different molecules are made to crystallise with each other, the probability of heteromeric crystallization is more as compared to homomeric crystal formation.Hence, it is expected that when valsartan and sacubitril are combined together in a mediam, they would readily form a co-crystal/complex in a specific ratio in presence of and with th eco- formers sodium and water.

Thus, taking the teachings of WO'345, US996, WO'253, Morisette et al, Christer et al and other prior arts, it would be obvious for a person skilled in the art to arrive at the supramolecular compounds as claimed in the impugned application.

The impugned patent application provides no technical advancement as compared to the composition of WO'345. As discussed in preceding paragraphs, WO345 teaches that Valsartan and Sacubitril together reduces the dose and dosage of both the drugs as compared to valsartan monotherapy or sacubitril monotherapy. WO345 also teaches that the advent of side effects is lesser with
the combined use of Valsartan and Sacubitril as compared to monotherapy with either of the drugs.

The Applicant stated in their reply statement that the technical advancement of the claimed complex of Valsartan and Sacubitril possesses technical advancement over a physical mixture of Valsartan and Sacubitril in terms of better bioavailability, lesser hygroscopicity, increased water solubility/dissolution, and better stability.

As discussed in detail in preceding paragraphs the prior art documents US996 and especially WO253 disclose that the salt hydrate forms of said APIs possess better bioavailability, lesser hygroscopicity, increased water solubility/dissolution, and better stability as compared to Valsartan free acid, Valsartan disodium amorphous form, and Sacubitril free acid.

Thus, the prior art already taught that conversion of Valsartan and Sacubitril into crystalline salt hydrate forms results in improvement in various properties such as better bioavailability, lesser hygroscopicity, increased water solubility/dissolution, and better stability.
Further, the Applicant submitted no argument and/or document in reply statement to establish any improvement in therapeutic efficacy of claimed complex of Valsartan and Sacubitril over physical mixture of Valsartan and Sacubitril.
After almost two years of filing the reply statement without any evidence, the Applicant belatedly filed some documents and evidences of Dr.Myerson, Dr. Michael and Dr. Gauri Billasupposedly in support of inventive step of the claimed invention.
Dr. Motto has stated in his affidavit that various approaches were tried for combining Valsartan and Sacubitril such as mixed anhydride approach, n-acyl tetrazole approach, imide approach etc which were not successful.

It is submitted that before the priority date of the impugned application, the physicochemical properties of both Valsartan as well as Sacubitril were well known which is also evident in the disclosure of US996 and WO253. People in the field were aware that both the drugs have poor solubility and bioavailability issues. in light of this knowledge a PSITA will not embark on combining Valsartan and Sacubitril by the approaches mentioned by Dr. Motto since all these approaches lead to formation of a very large molecule which a PSITA understands will have even more solubility and bioavailability issues as compared to Valsartan and Sacubitril. The fact that all these approaches lead to a very large molecule is also depicted in the diagrams presented in Dr. Motto's affidavit.

. Further, prior art documents US996 and WO253 teach that solubility and bioavailability issues associated with Valsartan and Sacubitril can be resolved by converting them into crystalline salt hydrate forms.WO253 prior art document also teaches that the two drugs can be combined and that the drugs of such combination can be converted into crystalline salt hydrate form by a common process by dissolving in a solvent and reacting with corresponding base followed by equilibration or seeding.

In view of such knowledge in the field PSITA is motivated to first try formation of crystalline salt hydrate form of the two APIs as taught in the prior art. It is submitted that the approach adopted by inventors of impugned application is same as that taught by prior art WO253 is also established by the fact that the process of preparation exemplified in impugned application is same as that taught by WO253 and US996.

Dr. Motto further states that various cations such as calcium, magnesium, iron, zinc, ammonia, sodium were experimented with in trivalent, divalent, monovalent salts using various solvents and solvent combinations.

However, WO345 and US996 teach PSITA that the preferred salt form of Sacubitril is sodium. Hence, to form a combination of Valsartan and Sacubitril, PSITA is motivated to choose a cation which will be common to both Sacubitril and Valsartan since 1. it will be easier to prepare such combination by reacting both Valsartan and Sacubitril with the same base, and 2. Presence of common ion leads to decreased chances of incompatibilities which translates into higher expectation of successful formation of the co-crystal.

Further, WO253 teaches PSITA that sodium form of Valsartan is amorphous while disodium salt form of Valsartan, especially disodium hydrate form of Valsartan is crystalline with high stability, low hygroscopicity, and high dissolution. Thus, WO253 also teaches that crystalline salt form is better than amorphous salt form due to various reasons listed therein.

Furthermore, the process of preparation of Sacubitril sodium and Valsartan disodium hydrate form with 2.4$\pm$1 water is taught by US996 and WO253, including the process of crystallization by solvent evaporation and/or seeding and/or equilibration. The solvents to be used in each step of process are also disclosed in WO253.

. Based on above reasons PSITA is motivated to first form salt of Valsartan and Sacubitril using sodium cation in the stoichiometry taught in prior art as well as through the process and solvents taught in prior art.

. Dr. Motto has stated that the claimed complex possesses unexpected properties in terms of crystallinity, low hygroscopicity, stability, solubility, improved bioavailability. Further, Dr. Motto has compared the hygroscopicity of sodium salt of Sacubitril and disodium salt of Valsartan with that of the complex LCZ696.

As discussed above, WO253 and US996 disclose that the hydrate forms of Sacubitril sodium and Valsartan disodium are more stable, and less hygroscopic than non hydrate form of Sacubitril sodium and Valsartan disodium. The prior art documents also disclose that the hydrate salt forms are crystalline, have low hygroscopicity, have good stability, solubility, improved bioavailability.

. Based on the US FDA Prescribing Information of Entresto as well as study Gu et al, Dr. Motto has stated that bioavailability of the supramolecular complex is higher than Valsartan and therefore, lesser amount of Valsartan is required when supramolecular complex is used as compared to Valsartan (Diovan).

. It is submitted that Diovan is the marketed preparation of Valsartan which contains Valsartan free acid and not salt form. WO345 disclosed that when Valsartan or its pharmaceutical salt is combined with Sacubitril or its pharmaceutical salt, the dose and dosage of Valsartan and Sacubitril is reduced as compared to Valsartan or Sacubitril alone.

Thus, decrease in dose of the API, decrease in hygroscopicity, increase in bioavailability, better stability, enhanced solubility of the of the hydrate salt forms of Valsartan and Sacubitril together are obvious traits in view of the disclosure of the prior art documents discussed above.

Dr. Myerson has stated in his affidavit that formation of a supramolecular compound of two pharmaceutically active molecules (such as valsartan andsacubitril), in particular of two such molecules in anionicform linked together via a cationic linking moiety (such assodium) and water molecules, would not have been considered by the skilled person as a routine approach for drug development at the priority date.

However, both WO345 and WO253 teach PSITA to combine Valsartan and Sacubitril and react these APIs with corresponding base to form crystalline salt hydrate form and that the water in these hydrate salt forms interacts with the APIs and cations by strong intermolecular forces (i.e. non-covalent bonds) and thereby becomes an integral part of the crystal lattice. The relevant paragraphs from WO253 and WO345 have been quoted in preceding paragraphs and the pertinent line therein have been highlighted. Further, it is common knowledge to PSITA that in salt form the charged API molecules form ionic bonds with the cation and the water of the hydrate. Thus, before the priority date of the impugned application it was known to PSITA that Valsartan and Sacubitril can be processed together by same process of reacting them with corresponding base to form crystalline salt form, and that this resultant crystalline salt hydrate form will have the API molecules, cation molecules, and water molecules bonded together by non covalent bondssuch as ionic bonds, and other strong intermolecular forces.

Dr Myerson has stated that formation of a co-crystal which has different molecules interacting together by non-covalent bonds was not known at the time of the invention.

It is submitted that prior art documents such as Morissette and Christer teach formation of several cocrystals, the mechanism of bonding in these co-crystals, as well as general scheme of synthesis of co-crystals. Said documents reveal that molecules and ions in solution interact with each other to form to neutralize each other's charges and that this interaction is by non-covalent bonds such as ionic bonds, hydrogen bonds, and van-der-waals forces resulting in a stable co-crystal.

The disclosure of said prior art documents read along with the teachings of WO345, WO253, US996 make the claimed complex obvious to a PSITA wherein it is understood by a PSITA that sodium and water molecules act as co formers to form the crystal along with Valsartan and Sacubitril molecules.

Dr, Myerson has stated that prior art documents teach different doses of Valsartan and Sacubitril. However, supramolecular complex dictates Valsartan and Sacubitril to be in strict 1:1 molar ratio, which is not taught by prior art documents.

It is submitted that prior art documents WO345 and WO253 teach that valsartan and sacubitril can be combined and processed with a corresponding base to form crystalline salt hydrate form. It is submitted that the stoichiometery of the two APIs is governed by the chemical property of the molecules rather than the dose to be given to a patient. Therefore, firstly there is no correlation between the dose of the two APIs and there stoichiometry in the complex, secondly the stoichiometry of the two APIs is taught in the prior art that Sacubitril sodium hydrate and Valsartan disodium hydrate are the preferred forms of both the APIs and they are to be processed in same manner to prepare the salt form which inevitably results in Valsartan and Sacubitril combining in 1:1 ratio.

Further, Dr.Myerson has reiterated the Applicant's submissions of reply statement with respect to each of the prior art documents discussed by the Opponent.

The specific disclosure, teachings, and motivation from the prior art documents cited by the Opponent as well as response to Applicant's contentions with regard to said documents have been discussed in detail in preceding paragraphs and are not being repeated herein for sake of brevity.

Dr. Billa elaborates on the clinical trial evidence and the nature of Vymada as a breakthrough drug. She neither compares the efficacy produced by Vyamada with Valsartan and Sacubitril administered together nor does she state in any manner that the therapeutic efficacy of the Vymada is better than therapy with Valsartan and Sacubitril administered together.

The Applicant has relied on publications of Gu et al, McMurray et al, and Izzo et al to establish the enhancement in therapeutic efficacy of the complex of Valsartan and Sacubitril and has stated that less dose of Valsartan is required with the complex as compared to Valsartan alone.

It is submitted that WO345 discloses that when Valsartan and Sacubitril are given in combination the dose, dosage, and side effects are reduced as compared to monotherapy with either Valsartan or Sacubitril. The publications of Gu et al and McMurray et al disclose same teaching as that of WO345.

The document of Izzo et al, a publication by the Applicant, states that when the complex LCZ696 is used as compared to physical mixture of Valsartan and Sacubitril, the effect produced is similar and the dose of Valsartan required is less.

However, as explained in detail under the ground of non-patentability under Section 3(d) an analysis of the quantified data presented in the paper reveals that reduction in amount of Valsartan in LCZ696 lead to concurrent reduction in the observed therapeutic effect as compared to physical mixture of Valsartan and Sacubitril and in fact, almost double dose of Sacubitril is required in LCZ696 to produce the same level of effect as that produced by physical mixture of Valsartan and Sacubitril. Therefore, the complex is actually inferior to physical mixture of Valsartan and Sacubitril in terms of therapeutic effect.

As such, on account of lack of comparative data and lack of establishing any technical advancement, the claims are obvious and devoid of inventive merit.

The opponent 4 (Dr. Reddy's Laboratories Ltd.) submitted that D3 (EP0443983) discloses and claims valsartan for the first time. It is submitted that the compound valsartan as disclosed in the present prior art has the IUPAC name (S)-N-valeryl-N-{[2'-(1H-tetrazole-5-yl)- biphenyl-4-yl]-methyl}-valine). The present prior art also discloses the method of manufacture of the claimed compounds and specifically valsartan **.**

Applicants (NOVARTIS AG.)Arguments and Submission on D3 (W02/06253)

The Applicant submitted that there is no reference of any combination of **Valsartan with Sacubitril in WO '253 let alone the compound claimed in the IN '4412 application.**

The Applicant argued ithat *the document **D3, WO '253, relates to simple salts of***

***Valsartan and provides no relevant teaching towards the invention**. It is irrelevant that WO'253 discloses a sodium salt of Valsartan because WO'253 does not disclose any combination of Valsartan (or a sodium salt of Valsartan) with Sacubitril. WO'253 therefore provides no relevant teaching towards the invention.*

***The applicant argued** that a person skilled in the art would not have selected Valsartan disodium salt from WO '253 for various reasons as given below.*

In any event, Valsartan, in an approved form (Diovan & Co-Diovan) is present as free acid, i.e., not as a salt and this well-known free acid form would have been the obvious route for the skilled person looking to develop Valsartan. Therefore, a person skilled in the art would be inclined to use well-known free acid form to develop Valsartan or its combination.

The law in relation to inventive step is that a teaching of a prior art has to be seen as a whole rather than cherry picking references arbitrary (*Roche vs CIPLA, RFA 92/2021, page 58*). WO '253 provides a laundry list of salts of Valsartan. However, a person skilled in the art (POSA) will read this document as a whole and upon reading the document recognize that calcium tetrahydrate and magnesium hexahydrate are "particularly preferred" due to their "exceptional physical stability" (*page 4, middle §; page 6, 5th paragraph; also, other "outstanding" properties on pages 7, 15 and 23*).

Further, **WO '253 at pages 7, 15 & 23 clearly reports that the said two salts have water solubility several times better than that free acid of Valsartan**, have high melting point and excellent chemical and physical stability and is suitable for pressing directly to form corresponding tablet formulation and has advantageous properties such as uniform crystal conglomerates which can be used in the galenic formulation.

Further, no such advantageous properties are attached to sodium salt – to the contrary sodium salt has poor physical properties.

a) Example 5 (page 47) describes disodium Valsartan as "hygroscopic".

b) Example 11 (page 51) describes a disodium Valsartan hydrate which is "slightly hygroscopic" and ill-defined stoichiometry (2.4 ± 1.0 moles).

Thus, a person skilled in the art would be motivated to use the calcium/magnesium salt of Valsartan and not the disodium salt particularly when the said disodium hydrate salt of Valsartan is hygroscopic ***(pages 47 & 52, §1)*. Further, the formulation example 1 and 2 disclosed in WO'253 at *pages 59 and 60*** provide a tablet with calcium tetrahydrate and magnesium hexahydrate.

Also, ***Dr. Michael Motto*** *in para 17* states that during the research, the inventors recognized that to form a double salt with monovalent cations seemed scientifically non- viable and counter intuitive and therefore a person skilled in the art would not have selected a sodium cation to make a single compound containing Valsartan. [P.S Valsartan is a diprotic acid and therefore there was a clear teaching to a divalent salt (Ca or Mg)] instead of a monovalent salt (Na, K).

Therefore, a person skilled in the art would be motivated to use calcium tetrahydrate and magnesium hexahydrate and will be taught away from using a monovalent salt such as a sodium salt of Valsartan. This is notwithstanding the fact that in the present invention, the single entity/ compound of Valsartan and Sacubitril with trisodium cation. (*please see page 46 of the patent specification).*

(E) SUBMISSION OF THE APPLICANT: NO MOTIVATION FOR A POSA TO ARRIVE AT THE COMPOUND CLAIMED IN IN '4412 FROM THE TEACHING OF ALMARSSON, MORISSETTE AND VISHWESHWAR

The Applicant submits that in the pharmaceutical field at the priority date, co-crystals formed between a neutral API molecule and a co-crystal former ("co-former") molecule were referred to as "pharmaceutical co-crystals" and were considered a new and unexplored class of materials at the priority date. A co-former was typically a structurally simple, neutral molecule that could act as an inert additive to assist in the formation of a crystal. As reflected in the following citations of the Opponent, and as explained by *Dr Myerson at paras 3.1-3.3*, the formation of pharmaceutical co-crystals involving an API and a co- former was unpredictable, and they were not used as a matter of routine in drug development at the priority date. Pharmaceutical co-crystals involving two APIs were even more unusual.

Indeed, at the priority date, there were no pharmaceutical designated supramolecular compounds containing two different active ingredients approved for heart failure or hypertension. Applicant's drug ENTRESTO/VYMADA containing the claimed compound is the **first ever** approved pharmaceutical supramolecular compound containing two active ingredients for the treatment of heart failure.

The applicant argued that none of the Opponent's citations relates to a supramolecular compound comprising two anionic moieties, let alone two anionic APIs. The Opponent has clearly used impermissible hindsight in their arguments.

As reflected in the following citations of the Opponent, and as explained by ***Dr Myerson at paras 3.1-3.3,*** **t**he formation of pharmaceutical co-crystals involving an API and a co-former was unpredictable, and they were not used as a matter of routine in drug development at the priority date. Pharmaceutical co-crystals involving two APIs were even more unusual. Indeed, at the priority date, there were no pharmaceutical designated supramolecular compounds containing two different active ingredients approved for heart failure or hypertension. Applicant's drug ENTRESTO/VYMADA containing

the claimed compound is the **first ever** approved pharmaceutical supramolecular compound containing two active ingredients for the treatment of heart failure.

The applicant argued that none of the Opponent's citations relates to a supramolecular compound comprising **two anionic moieties**, let alone two anionic APIs. The Opponent has clearly used impermissible hindsight in their arguments.

NON-PATENT LITERATURE

NON-PATENT LITERATURE WHICH PROVIDES STUDIES ON ALTERNATIVE SOLID FORMS, PARTICULARLY SUPRAMOLECULAR COMPLEXES AND CO-CRYSTALS – WHICH WERE KNOWN TO HAVE SUPERIOR PHYSICAL PROPERTIES:

D4 (Morissette et al.) - High-throughput crystallization: polymorphs, salts, co-crystals and solvates of pharmaceutical solids:

D4 is an article on HT screening and crystallization and its use in the pharmaceutical discovery process. **(REP –pg 205)** It is a natural endeavour in pharmaceutical sciences to prepare solid forms as they provide many advantages (pg. 276 D4, REP –pg 206) Where stable crystal forms fail to have advantages, alternative solid forms are investigated.
It discusses engineering of co-crystals at3.5 (pg. 292; pg 222 of REP)
Co-crystals of drugs and drug candidates represent a new type of material for pharmaceutical development. They are part of a broader family of multicomponent crystals that also includes salts, solvates, clathrates, inclusion crystals and hydrates as shown in Scheme 2. The primary difference between solvates and co-crystals is the physical state of the isolated pure components: if one component is a liquid at room temperature, the crystals are designated as solvates; if both components are solids at room temperature, the crystals are designated as co-crystals. While at first glance these differences may seem trivial, they have profound impact on preparation, stability and ultimately on the ability to develop products.

Co-crystals have been prepared by melt-crystallization, grinding and recrystallization from solvents [1] *Solvent systems for co-crystals must dissolve all components, but must not interfere with the interactions necessary for cocrystal formation.* ***The need to try many solvent combinations and the availability of multiple co-crystal formers creates a diversity that is ideally suited for exploration by HT systems. Co-crystals have the potential to be much more useful in pharmaceutical products than solvates or hydrates. The number of pharmaceutically accept˘able solvents is very small, and because solvents tend to be more mobile and have higher vapor pressure, it is not unusual to observe dehydration/ desolvation in solid dosage forms. Solvent loss frequently leads to amorphous compounds, which are less chemically stable and can crystallize into less soluble forms. In contrast, most co-crystal formers are unlikely to evaporate from solid dosage forms, making phase separation and other physical changes less likely.***

Left column, page 294 (page 224 of REP)

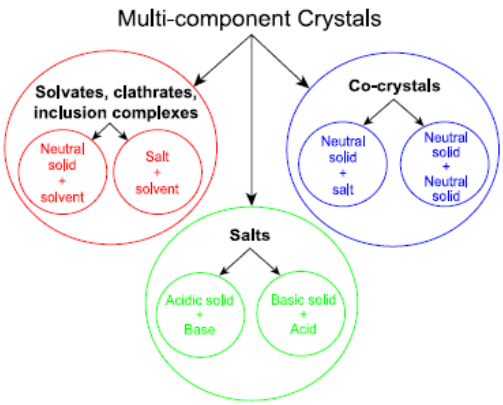
The above studies focused on demonstrating the use of supramolecular synthons to create novel crystalline phases. The variety of structures observed provides hope that some forms will have superior performance in pharmaceutical dosage forms. However, the studies stop short of providing data on the physical properties, such as solubility, necessary to evaluate their utility. Furthermore, only the saccharin and nicotinamide co-crystals of carbamazepine represent

pharmaceutically acceptable co-crystals. Crystals containing two drugs may appear to be a good technique for making combination products of two drugs, but unless the two drugs are dosed only in stoichiometric ratios consistent with the co-crystal composition, such crystals would still need to be co-formulated with at least one of the bulk drugs in order to satisfy the clinical requirements. Therefore, a skilled person aiming at providing stable solid forms would opt for co- crystal formation when physical mixtures of such compounds were already taught in prior art.

Left column, page 294 (page 224 of REP)

The above studies focused on demonstrating the use of supramolecular synthons to create novel crystalline phases. The variety of structures observed provides hope that some forms will have superior performance in pharmaceutical dosage forms. However, the studies stop short of providing data on the physical properties, such as solubility, necessary to evaluate their utility. Furthermore, only the saccharin and nicotinamide co-crystals of carbamazepine represent pharmaceutically acceptable co-crystals. ***Crystals containing two drugs may appear to be a good technique for making combination products of two drugs, but unless the two drugs are dosed only in stoichiometric ratios consistent with the co-crystal composition, such crystals would still need to be co-formulated with at least one of the bulk drugs in order to satisfy the clinical requirements.*** **Therefore, a skilled person aiming at providing stable solid forms would opt for co- crystal formation when physical mixtures of such compounds were already taught in prior art.**

D4 describes designing and preparing alternative crystalline forms like co-crystals where the convention crystal forms fails to have the desired effect. It discloses that It is a natural endeavour in pharmaceutical sciences to prepare solid formsas they provide many advantages (pg. 276) . It discusses engineering of co-crystals at3.5 , page 292, teaches that co-crystals of drugs and drug candidates represent a new type of material for pharmaceutical development. They are part of a broader family of multicomponent crystals that also includes salts, solvates, clathrates, inclusion crystals and hydrates as shown in Scheme 2.



Scheme 2. Types of multicomponent crystals.

It also discloses at the left column, page 294 that crystals containing two drugs may appear to be a good technique for making combination products of two drugs, but unless the two drugs are dosed only in stoichiometric ratios consistent with the co-crystal composition, such crystals would still need to be co-formulated with at least one of the bulk drugs in order to satisfy the clinical requirements. In the present case, the doses of Valsartan and Sacubitril were well known in prior art including D1 and a skilled person can easily comprehend the stoichiometric ratios without any undue experimentation.

The opponent 4 submitted that the prior art **document D4 US 5217996** discloses the compound which acts as NEP inhibitor and which can be used as antihypertensive saluretic agents, and specifically in the examples 7 and 8 and claim 6, teaches the sodium salt of the sacubitril [N-(3- Carboxy-1-oxopropyl) -(4S)-p-phenyl phenyl methyl)-4-amino2R- methyl butanoic acid, ethyl ester].
(Reference: column 18, lines 59 to 64 of document D4)

The applicant submitted that Morissette is a review article on high-throughput crystallization that discusses engineering of single API co-crystal.

Morissette recognizes that the formation of pharmaceutical co-crystalsinvolvingONE API andaco-formerwasunpredictableandnot a matter of routine in drug development at the priority date *(page 276 RHS last para)*. In particular:

a) Morissette recognizes that despite centuries of research the fundamental mechanisms and molecular properties that drive crystal form diversity, specifically the nucleation of polymorphic forms, are **not well understood** and therefore **predictive methods** for accessing behavior remains a **formidable challenge** *[page 276, RHS, last para]*.

b) T**he prediction** of packing structures for multicomponent (e.g., solvates, hydrates, co-crystals) or ionic systems **is not yet possible** *[page 277, LHS, first para]*.

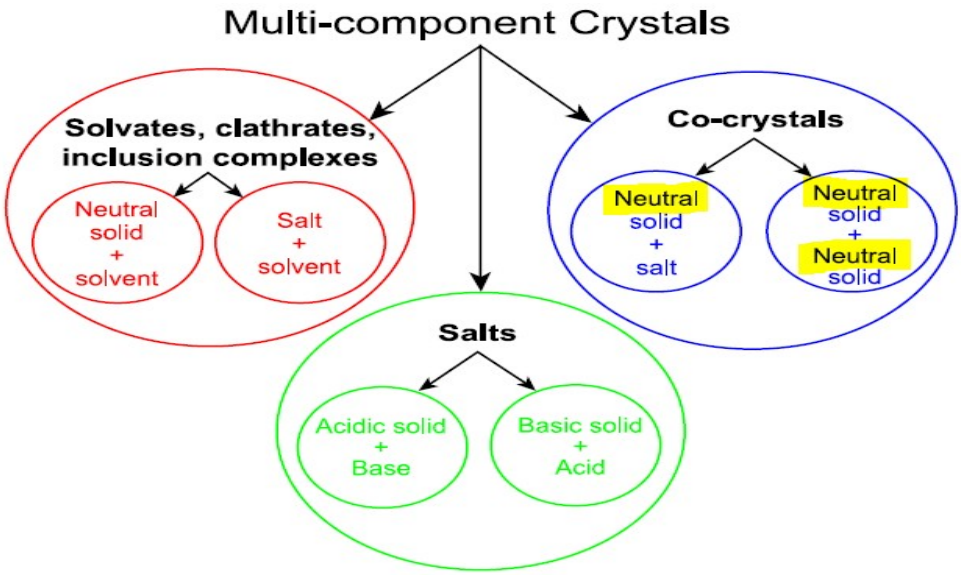
c) Morissette also focusses on co-crystals containing only one API with a co- former whereas in the present invention the novel compound has 2 APIs with NO co-former. There is no example of a 2API co-crystal being used successfully.

d) The article further demonstrates unpredictability in the art: "*The existence and identity of hydrates, solvates, co-crystals and polymorphs have* ***defied prediction"*** and "*in general*

discrete crystal forms are considered ***non-obvious*** ***and patentable"****. page 296 (RHS, last para)*

Further, Morissette's definition of co-crystal teaches away from the claimed supramolecular compound. Para 4.16 of Dr. Myerson's affidavit**:**

a) States that at least one component of a co-crystal should be "Neutral" (i.e., **non ionized**, scheme 2, page 293)



Scheme 2. Types of multicomponent crystals.

The applicant argued *that therefore teaches away from and excludes the claimed compound of IN'4412 as it has: (i) both Valsartan & Sacubitril present in* ***anionic form*** *and all carboxylic acid groups are present in ionized form; (ii) sodium cations.*

D5 (Almarsson et al.) (page 1889, pg 231 of REP) is an article on the evolution of crystal engineering into a form of supramolecular synthesis and the problems and opportunities in the pharmaceutical industry. Specifically, it has become clear that a wide array of multiple component pharmaceutical phases, so called pharmaceutical co-crystals, can be rationally designed using crystal engineering, and the strategy affords new intellectual property and enhanced properties for pharmaceutical substances.

Column 2 (page 1889, pg 231 of REP)
What are pharmaceutical co-crystals?
Herein we define pharmaceutical co-crystals as being a subset of a broader group of multi˘component crystals that also includes salts, solvates (pseudopolymorphs), clathrates, inclusion crystals and hydrates. In a supramolecular context, solvates and pharmaceutical co-crystals are related to one another in that at least two components of the crystal interact **by hydrogen bonding and, possibly, other non covalent interactions rather than by ionpairing. Neutral compounds and salt forms alike have the potential to be solvated (i.e. interact with solvent molecules) or co-crystallized (i.e. interact with a co-crystal former).** Solvate molecules and co-crystal formers can include organic acids or bases that remain in their neutral form within the multicomponent crystal. The primary difference is the physical state of the isolated pure components: **if one component is a liquid at room temperature, the crystals are referred to as solvates; if both components are solids at room temperature, the products are referred to as co-crystals.** While at first glance these differences may seem

inconsequential, they have profound impact on the preparation, stability, and ultimately on developability of products. Furthermore, whereas solvates are commonplace because they often occur as a serendipitous result of crystallization from solution, co-crystals, especially pharmaceutical cocrystals, represent a relatively unexplored class of compounds. **On the other hand, as will become clear herein, pharmaceutical co-crystals can be rationally designed and there are many more potential co-crystal formers than there are solvents or counter ions.**
Therefore, **D5 (Almarsson et al.)** discusses the evolution of crystal engineering into a form of supramolecular synthesis and the problems and opportunities in the pharmaceutical industry. It defines pharmaceutical co-crystals as being a subset of a broader group of multi-component crystals that also includes salts, solvates (pseudopolymorphs), clathrates, inclusion crystals and hydrates. In a supramolecular context, solvates and pharmaceutical co-crystals are related to one another in that at least two components of the crystal interact by hydrogen bonding and, possibly, other non-covalent interactions rather than by ion-pairing. Page 1894 (pg 236 of REP).

The opponent no 4 (Dr. Reddy's Laboratories Ltd.) submitted that **D5 WO 02/06253** relates to new salts of valsartan or crystalline, also partly crystalline and amorphous salts of valsartan, the respective production and usage, and pharmaceutical preparations containing such a salt. It is submitted that D5 specifically intends to meet the need in the art for more stable crystalline forms of valsartan and teaches towards salts of valsartan which are selected from the group consisting of the monosodium salt, the disodium salt, the monopotassium salt, the dipotassium salt, the magnesium salt, the calcium salt, the bis-diethylammonium salt, the bis- dipropylammonium salt, the bis-dibutylammonium salt, the mono-L- arginine salt, the bis-L-arginine salt, the mono-L-lysine salt and the bis-L-lysine salt, as well as salt mixtures, or respectively, an amorphous form, a solvate, especially hydrate, as well as a polymorphous form thereof, the respective production and usage, and pharmaceutical preparations containing such salts.

The opponent no 4 (Dr. Reddy's Laboratories Ltd.) submitted that **D5 discloses** that the preferred salts of valsartan are selected from the mono-sodium salt in amorphous form; di-sodium salt of valsartan in amorphous or crystalline form, especially in hydrate form, thereof.

Further, the present prior art also teaches salt mixtures are (i) single salt forms from different cations selected from the above group or (ii) mixtures of those single salt forms which exist for example in the form of conglomerates. Moreover, the present prior art also teaches the equilibrating crystallisation process for producing hydrates of valsartan. Therefore, in view of the above-mentioned prior art, any person skilled in the art will be motivated to crystallise di-sodium salts of valsartan for use as angiotensin receptor inhibitors.

The opponent no 4 (Dr. Reddy's Laboratories Ltd.) submitted that the document D5 establishes that the crystalline salt forms, especially crystalline salt hydrates of Valsartan have numerous advantages over Valsartan free acid. These advantageous

properties as leant from D5 by a person skilled in the art include better water solubility, higher stability, higher bioavailability, no water absorption or water loss which is less hygroscopicity, and therefore better stability. ***(Reference: page 3 and page 4 of document D5) (Reference: page 4, para 2 of document D5) (Reference: page 5, last para of document D5) (Reference: page 25, para 5 of document D5) (Reference: page 26, para 3 of document D5) (Reference: page 37, last para of document D5) (Reference: page 38, para 1 of document D5) (Reference: page 47, Example 5 of document D5)***

The opponent no 4 (Dr. Reddy's Laboratories Ltd.) submitted that the present opposition challenges the present application based on lack of technical advancement, which it fails to establish over what was already being researched and known in the art. The basis of the teachings and disclosures contained in various prior art documents cited by the Opponent, there was sufficient motivation for a person skilled in the art to develop the compounds/ molecular structures as disclosed and claimed in the impugned patent since it was already known that:-

§ Angiotensin receptor and NEP inhibitors can be used for treatment of heart failure/diseases;

§ Valsartan and sacubitril can be used in combination as Angiotensin receptor and NEP inhibitors respectively for the treatment of heart failure/diseases;

§ Valsartan and Sacubitril can be administered together, one after the other and/ or separately in one combined unit dose form and/or in two separate unit dose forms;

§ Valsartan and sacubitril are respectively most stable in their salt form;

§ Crystals of valsartan and sacubitril are superior in as much as they are more stable than amorphous forms thereof.

Applicant submission on D5
Almarsson et. al. 2004

The Applicant submitted that 'pharmaceutical co-crystals' were not well-known and were in their infancy at the priority date. The title of the said article "*Do pharmaceutical co-crystals represent a new path to improved medicines*?" is indicative of pharmaceutical co-crystals research being new on the priority date. Further, much of Almarsson is speculative in its approach.

The said **article does not teach towards** using co-crystals involving two APIs as a **routine approach for** providing combination therapies. Instead, Almarsson focusses on the design of co-crystals involving a single API and pharmaceutically inert co-former. [*Page 1894 (LHS)*].

a) **Co-crystals are not routine part of pharmaceutical research:**
Almarsson is a review article which states that pharmaceutical co-crystals "*represent a relatively* ***unexplored class of compounds***" *(p.* ***1890, page 1890, LHC, 1st §) and*** confirms that co-crystals were not a routine part of pharmaceutical research and development (***Para 4.20 of Dr Allan Myerson***).

b) **Co-crystal formation is of One API only and a co-former agent**:
Almarsson discusses the design of single API cocrystals. It only speculatively suggests a possibility of using an API that already is recognized as "eminently safe" in **sub-therapeutic amounts** as a co-former (i.e., the conformer API is not used as therapeutic agent) and stresses that this idea is "*provocative*". *(pg. 1894, LHC, final few lines),* ***para 4.22 of Dr. Myerson's affidavit****.*

The Applicant submits that Almarsson certainly does not teach the use of a supramolecular compound containing two APIs in therapeutic amounts (i.e., a dual acting compound).

Further, the definition of cocrystals in the said article *(page 1889, last §)* excludes interactions of the components of the crystal by ion pairing, i.e. the claimed compound does not even fall under Almarsson's definition and states the following:

"In a supramolecular context, solvates and pharmaceutical cocrystals are related to one another in that at least two components of the crystal interact by hydrogen bonding and other non-covalent bonding rather than ion-pairing" ***para 4.23 of Dr. Myerson's affidavit***

The applicant argued that the allegation of the Dr. Ramesh Dandala (paras 14 & 15) / Opponent that a skilled person would expect Valsartan and Sacubitril to form a supramolecular compound, in view of Almarsson and Morissette, and in view of the nature of Valsartan (containing a carboxylic acid moiety) and Sacubitril (containing both a carboxylic acid moiety and an amide moiety), is **illogical and unscientific** for the following reasons:

a) Valsartan and Sacubitril are ionized in the claimed compound and therefore do not contain any carboxylic acid groups.

b) Co-crystal formation is unpredictable and cannot be predicted merely based on functional groups present.

c) The presence of carboxylic acid and amide moieties in Sacubitril would only lead to the conclusion that it contains self-complementary groups and thus could crystallize on its own (self-organization) in its free acid form. Similarly, Valsartan has a tetrazole and carboxylic acid moiety, and this would similarly indicate that Valsartan could be crystalline on its own in its free acid form.

d) The supramolecular compound of the invention is held together by a network of non-covalent bonds, in particular ionic and hydrogen bonds, between anionic Valsartan and Sacubitril, sodium cation and water molecules.

The applicant further argued that *there is no teaching in Almarsson regarding a claimed compound containing two APIs in therapeutic amounts (i.e. a dual acting compound). Further, teaching of Almarsson does not extend to the claimed compound for the following reasons*

a) Co-crystals described in Almarsson contain one API and one co-former (which is not an API).

b) Almarsson itself states that a suitable co-former that may be employed is a "*solid material with GRAS* (generally regarded as safe) *status*" (*page 1894, left column*).

c) Almarsson only speculatively suggests the possibility of using a second API as a co-former, but stresses not only that this idea is "provocative", but also that the second API should be used in a **"sub-therapeutic amount"** (*p. 1894, left column).* The second API should be an "*eminently safe drug substances*" according to the said article (*p. 1894, left column*).

d) Clearly, Almarsson does not teach the use of co-crystals containing two APIs for delivery of combination therapy. This precludes the co-crystal being used to provide effective combination therapy.

e) Furthermore, Sacubitril would not have been considered at the priority date **because it had never been approved**. Therefore, any teaching that could possibly be derived from this publication does not extend to the claimed compound.

D6 (Vishweshwar et al.) -Crystal engineering of pharmaceutical co-crystals from polymorphic active pharmaceutical ingredients (pg 239 of REP)

D6 is an article on crystal engineering of pharmaceutical co-crystals from polymorphic active pharmaceutical ingredients. Pharmaceutical co-crystals address physical property issues. The discussion involves as to how carboxylic acids and amides form hydrogen bonds and illustrated the co-crystals formed by Piracetam with a combination of gentisic acid and p-hydroxybenzoic acid. In column 2 , at page 4601 (239 of REP) it teaches that single crystals of 1:1 co-crystal of piracetam and gentisic acid were obtained via slow evaporation from
It further teaches that co-crystals can be formed from grinding of slurrying in water. In page 4602 (pg 240 of REP) it discloses the various solvent which the solvents which were tested and used including acetone, water, methoanol, ethanol…."

D6 discloses that Pharmaceutical co-crystals address physical property issues. It further teaches that co-crystals can be formed from grinding of slurrying in water. In page 4602 (pg 240 of REP) it discloses the various solvent which the solvents which were tested and used including acetone, water, methoanol, ethanol…." Further D6 concludes that evaluation of new pharmaceutical co-crystals suggests that these co-crystals are robust enough to be prepared in solution, slurry or solidstate methods and appear less prone to polymorphism than corresponding single component. It does say that even though definitive conclusions cannot be made but that would not discourage a skilled person so much so that it would not even attempt to prepare the crystal form.

Applicant submission on D6, Vishweshwar et. al., July 2005

Vishweshwar describes the formation of a piracetam cocrystal with either gentisic acid or p-hydroxybenzoic acid, which are simple aromatic acids being used as co-formers not as therapeutic agents for combination therapy.

Further, all the components are in the neutral form. This will therefore teach away from the compound claimed by IN'4412 as it has

a) Anionic Valsartan;

b) Anionic Sacubitril; and c)

Cationic sodium.

Vishweshwar further recognizes that around the priority date co-crystals "**remain relatively unexplored"** (*page 4601*).

Vishweshwar has got nothing to do with Valsartan, Sacubitril or the compound of IN'4412 application. The formation of the simple compounds in Vishweshwar is not similar in any manner to the compound of the present invention.

The authors of Vishweshwar considered the carboxylic acid-primary amide supramolecular synthon to be the fundamental building block that binds their co-crystal together *(see page 4601, LHC, first paragraph and RHC, first paragraph).* Unlike piracetam (described in D6), neither Sacubitril nor Valsartan contains a primary amide group, nor do they have any other structural similarities with piracetam. Accordingly, there would have been no reason for the skilled person to reasonably expect that Valsartan and Sacubitril would form a supramolecular complex, in particular since the hydrogen bonds of a carboxylic acid-primary amide synthon as taught in D6 are not applicable to the present invention.

Futher the applicant submitted that *Dr. Michael Motto's affidavit clearly explains that various "experimental quests" were undertaken to combine Valsartan and Sacubitril into a single chemical entity* ***(Para 3 of Dr. Michael Motto's affidavit****) and that the formation of a single entity of two actives was challenging and not routine. This further goes to establish that the present invention is not obvious and requires extensive research.*

Dr. Michael Moto highlighted the extensive experimentation and research that led to the development of claimed compound. Various strategies were attempted unsuccessfully:

a) Mixed Anhydride approach

b) N-Acyl Tetrazole approach

c) Imide approach

d) Crystalline double salt formation approach

The applicant argued that the process to prepare the claimed compounds is **not routine** and developed after extensive experimentation and research (provides technological advancement). (***Paragraphs 3 to 17 of affidavit of Dr Michael Motto***).

SECTION 2(1)(j)(a)

The IN '4412 application provides the effects of both Valsartan and Sacubitril in a single compound which has several advantages:

a) One single compound comprising of both active ingredients inaratiowhich turnedouttobe thedesiredprecisestoichiometry at a fixed 1:1 molar ratio, is a **significant advantage**. **Novel single compound** comprising in which entities Valsartan and Sacubitril, in which entities are present in 1:1 stoichiometric ratio (*Gu et al filed with Dr. Motto's evidence*).

b) Both drug substances are present as a single compound which means that they will be simultaneously released after administration at the precise desired

stoichiometry (useful for therapeutic applications) as opposed to WO'345 wherein the chemical relationship between the individual active *substances* Valsartan and Sacubitril is left open. (*see, for instance, p. 15, second paragraph*)

c) A single compound is simpler to formulate and manufacture. When two separate compounds are co-formulated in a single drug product, excipients must be chosen which are compatible with each drug substance and the drug substances themselves must be chemically compatible when in physical contact.

The preferred embodiment in which x=2.5 (claims 2 and 3) additionally possesses the following advantages:

a) LCZ696 compound possesses a set of superior physico-chemical properties such as crystallinity, low hygroscopicity, stability, and solubility and demonstrates improved bioavailability in comparison to the separate active ingredients. (*page 8, 11 and 24 of the patent specification*)

b) **Economical advantage**: Less hygroscopic. Reducedhygroscopicity isakey featureofthe supramolecularcompoundwhichcombinestheconstituentsofthe compoundinasinglecrystalline phase.

c) LCZ696 is very stable with no degradation being observed after 1 week at 50˚ C –both for LCZ696 alone and in the presence of excipients –either in sealed containers or under 58% relative humidity. *(Feng et al)*

d) These physiochemical properties enable development of LCZ696 as a potentially promising **novel active ingredient in pharmaceutical products.**

{Refer to affidavit of Dr. Michael Motto (Paras 18-21, 25); Affidavit of Dr. Allan S. Myerson (Para 6.1, 6.2, 4.5) and Feng et al.}

LCZ696 IS NOT PREDICTABLE:

The Applicant submitted that it is unpredictable at the priority date whether a single compound - in particular, supramolecular compound - of Valsartan and Sacubitril would have existed at all. Further, the advantageous properties of the exemplified compound LCZ696 mentioned above (a representative compound of claim 1) could not have been predicted at the priority date.

Therefore, it is established that the compound disclosed and claimed in the IN' 4412 application is inventive over the prior arts cited in the present opposition as it possesses technical advantage and provides no teaching, suggestion or motivation to a person

skilled in the art to arrive at the present invention WITHOUT hindsight, which is impermissible in an obviousness analysis.

The compound subject matter of IN'4412 application and in particular as claimed in claims 2 & 3 (e.g., LCZ696) is the active ingredient used in commercially successful drug product marketed under the brand Vymada/Entresto.

Commercial product: Entresto® is a successful commercial product. The unusual, inventive approach is confirmed by the remarkable fact that the Applicant's drug ENTRESTO/VYMADA containing the claimed compound is believed to be the **first ever** pharmaceutical supramolecular compound containing two active ingredients approved for the treatment of heart failure. The said drug product is **the first-in-class angiotensin receptor-neprilysin inhibitor (ARNi**), approved in India for the treatment of heart failure (HF).

The applicant submitted that as stated by *Dr Gauri Billa in her affidavit* at paras 7 to 9 LCZ696 is now a **class I recommendation** for patients of HFrEF by both the American and European Heart Failure Guidelines (2016). It is the first approved drug in the class of ARNi, which is a **breakthrough in chronic heart failure therapy** and has a **unique mode of action which acts to enhance the protective effects** of the Natriuretic Peptide (NP) system while simultaneously suppressing the harmful effects of an overactive Renin Angiotensin Aldosterone System (or RAAS). LCZ696/Vymada is a breakthrough drug, particularly, considering that it is the first drug developed and approved in the class of ARNi for treatment of heart failure using the inventive combination of Valsartan and Sacubitril. The said drug, therefore, has proven therapeutic efficacy which has hitherto unknown. Sacubitril was never previously approved or developed as a drug and even today has never been approved as a monotherapy.

.

The applicant relies on following references:

a) Division Bench of the Delhi High court in Roche v/s Cipla, RFA (OS) 92/2012

Para 57. This argument ignores the fundamental truth about breakthrough inventions, which at the time they are invented may not be commercially the most viable for immediate marketing. They are useful and are industrially applicable as without them there would be no stepping stone to achieve the next lot of improvements.

The applicant submitted that the subject matter of the IN '4412 application has been granted patent in 70 countries. In *particular, very similar claims have been granted by the EPO in divisional patent EP2340828B1 (EP '828)* ***(filed with the patent office and enclosing again as Annexure- 2)***.

In particular, as in the pending claims of IN' 4412, the EPO divisional patent EP '828 claims the range x=0-3 and has a dependent claim to x=2.5. EP '828 claim 1 explicitly claims x=0-3 in the solid form and therefore corresponds to claim 1 in India. EP '828 claim 7 explicitly claims x=2.5 and therefore corresponds to claim 2 in India. Given that the EPO has granted very similar claims in EP '828 covering x=0-3 and x=2.5, the opponent's objection should be rejected. In addition, we confirm that the EPO parent patent, EP1948158B1, (claim 1 of which is similar to claim 3 of 4412 application) was maintained as valid in post-grant opposition proceedings

The applicant relies on Reference is made to the IPAB order in **OA/53/2020/PT/CHN (copy enclosed as *Annexure-3*)** wherein the IPAB in state that

"The submission that the appellant has reveals that corresponding US and EP applications have been granted is an indication that the inventions were found to have passed the tests of inventive step in those jurisdictions"

The applicant argued *that the preferred embodiment of the IN '4412 application has led to the development of a commercially successful drug, Entresto/Vymada®. Besides the claimed invention fulfilling the criteria of patentability, the claimed compound also satisfies the criteria of secondary consideration.*

a) Regulatory approval in 115 countries and launched in 100+ countries

b) Entresto® is a long-awaited **breakthrough** in the treatment of heart failure.

c) It is the first approved treatment for reduced ejection fraction heart failure in over ten years and is a **gamechanger** (Medpage Today, 5 Game-Changers in Cardiology in 2015: Entresto, see: http://www.medpagetoday.com/cardiology/chf/55415). [Para 9 of Dr. Gauri Billa's affidavit]

d) Clinical Trials in Entresto® 200 mg twice a day was stopped prematurely because of its **"overwhelming benefit"** (J.J.V. McMurray et al., The New England Journal of Medicine, 371 (2014), 993).

e) Entresto® is the first and only regulatory approval of Sacubitril. In other words, Sacubitril has not been approved till date as a monotherapy and was approved for the first time in Entresto®.

In this regard, reference has been made to the case ***Roche v/s Cipla, RFA (OS) 92/2012, page 58, para 106***

Besides the primary consideration as noted, the objective indicia of non- obviousness include secondary considerations such as (i) a long-felt need; (ii) failure of others; (iii) industry acclaim; and (iv) unexpected results.

In para 49 page 29 submission dated 20/09/2022 the opponent argued that D1 (WO 2003/059345) relates to a pharmaceutical composition comprising a combination of (a) AT-1 antagonist and (b) a NEP inhibitor, each of which are disclosed only as separate individual compounds. D1 also claims a kit comprising separate containers in a single package pharmaceutical composition, comprising in one container a pharmaceutical composition comprising a NEP inhibitor and in a second container a pharmaceutical composition comprising AT 1 antagonist. Applicant's reply to the objection in the Examination Report in which present D1 was cited as D2.

Without prejudice, in view of the following additional submissions in respect of inventive step, the instant objection is liable to be waived:

1) The person skilled in the art at the priority date of the application would understand the pharmaceutical composition as described in D2 as a combination of individual active ingredients in the form of a heterogeneous mixture of the respective compounds. In contrast, the present invention claims a unique compound combining the active components into a supramolecular structure.

2) The chemical structure of the claimed compound is highly intricate and is stabilized by an involved network of ionic, hydrogen and coordination bonds, which has been described in various ways in the specification. The representative compound consists of six anions of AT-1 antagonist, six anions of NEP inhibitor, 18 sodium cations, and 15 molecules of water, resulting in the molecular formula $C_{288}H_{330}N_{36}Na_{18}O_{48}\cdot 15H_2O$. Thus, it can be seen that the claimed compounds have a supramolecular structure distinct from the composition claimed in D2 and cannot be said to be obvious in view of teachings of D2.

3) The claimed process provides a unique synthesizing route resulting in a unique supramolecular compound wherein the two anionic moieties are linked together with non-covalent bonds to form a single large and highly intricate molecular structure. It is submitted that synthesizing such a compound was unknown as on the priority date of the present application. In any case, the process of D2 either alone or in view of the processes disclosed in other cited prior art documents cannot be said to motivate a person skilled to arrive at the claimed process, as on the priority date of the present application.

In para 51 reply submission dated 20/09/2022 page 29-30 the opponent 2 submitted *his interpretation that IT IS ADMITTED BY THE APPLICANT THAT D1 INCLUDES ALL COMBINATIONS OF VALSARTAN AND SACUBITRIL. IN OTHER WORDS, A SKILLED PERSON IN VIEW OF THE DISCLOSURE OF D1 CAN ENVISAGE THE SUPRAMOLECULAR FORM OF THECOMBINATION. THE APPLICANT OUGHT TO BE ENTITLED FOR PROTECTION OF FURTHER RESEARCH LEADING TO THE SUPRAMOLECULAR STRUCTURE 5 OF THE PRESENT INVENTION ONLY IF IT IS ABLE TO SUBSTANTIATE BASED ON EXPERIMENTAL DATA THAT THE EFFICACY OF THE CLAIMED COMPOUND IS MUCH SUPERIOR TO THE EXPECTED AND ANTICIPATED BENEFITS, WHICH A SKILLED PERSON CAN EXPECT. THAT THE EFFECT MUST BE UNPREDICTABLE AND UNEXPECTED. THERE IS NOT EVEN AN IOTA OF DATA TO ESTABLISH SUCH UNEXPECTED FINDINGS.*

In para 57-59 reply submission dated 20/09/2022 page 30-31 *the opponent 2 argued that the efficacy of the combination of Valsartan and Sacubitril was well known at the time of the invention particularly in the TREATMENT OR PREVENTION OF HEART FAILURE SUCH AS (ACUTE AND CHRONIC) CONGESTIVE HEART FAILURE) In this respect, the Opponents refers to the data submitted in Annexure II , annexed to the Reply Statement filed on March 3, 2017. The Opponent states that firstly the veracity of the data is questionable as the additional data was presented as a mere Annexure and not by way of an affidavit. The study provides results of a randomized, double blind, placebo-controlled , active comparator study.*

The INTERPRETATION as provided at page 43 states

Compared with valsartan, dual-acting LCZ696 provides complementary and fully additive reduction of blood pressure, which suggests that tlie drug holds promise for treatment of hypertension and cardiovascular disease.

In view of the admitted position that D1 covers all combinations of valsartan and sacubitril, it was all the more incumbent 5 on the Applicant to provide comparative data with the known form of Valsartan and Sacubitril together for which efficacy is also known, at the least, to establish enhanced therapeutic efficacy.

The Opponent 2 relies on the **Order dated July 20, 2021, of the Hon'ble Division Bench of the Delhi High Court in FAO (OS) (COMM); ASTRA ZENECA AB & ANR versus INTAS Pharmaceuticals Ltd., handed out at the hearing, which in Paragraph 29, and 30** *(copies handed out at the hearing)* highlight that **the tests for Obviousness and inventive step in such a situation where the prior art if of the Applicant is not "person of ordinary skill in the art" but rather "person in the know"**.

The opponent 2 submitted that" the Applicant placed **reliance on Izzo et al**. , annexure to **Dr. Allan S. Myerson, which is a 2017 publication on "Efficacy and Safety of Crystalline Valsartan/Sacubitril (LCZ696)** Compared With Placebo and Combinations of Free Valsartan and Sacubitril in Patients With **Systolic Hypertension**: The RATIO Study"Izzo et al. compared the systolic blood pressure (SBP)- lowering efficacy and safety of crystalline valsartan/sacubitril (LCZ696, an angiotensin receptor blocker– neprilysin inhibitor) 400 mg daily against valsartan (320 mg once daily) alone or
coadministered with placebo or increasing doses of free sacubitril (50, 100, 200, or 400 mg once daily) to identify the optimal antihypertensive combination dose. It further states that the SBP reduction with LCZ696 400 daily was similar to coadministered free valsartan 320 mg and sacubitril 200 mg. Effects were similar in those older and younger than 65 years, and active therapies had adverse event rates similar to placebo. Izzo et al. concludes that crystalline valsartan/sacubitril 400 mg daily (1) is superior to valsartan 320 mg daily for lowering SBP, (2) **has similar efficacy to the combination of free valsartan 320 mg plus free sacubitril 200 mg**, (3) represents the optimal dosage for systolic hypertension in patients of any age, and
(4) is safe and well tolerated.

The opponent 2 argued that Izzo et al. fails to substantiate the contentions of the Applicant that the claimed compound has superior properties, which were unexpected and surprising. Izzo et al. concludes that crystalline valsartan/sacubitril 400 mg daily (1) is superior to valsartan 320 mg daily (i.e. valsartan per se) for lowering SBP – THAT THE COMBINATION WAS SUPERIOR TO VALSARTAN PER SE WAS KNOWN AT THE TIME OF THE INVENTION FROM THE DISCLOSURE OF D1.

The Opponent refers to Figure 2 in Izzo et al.

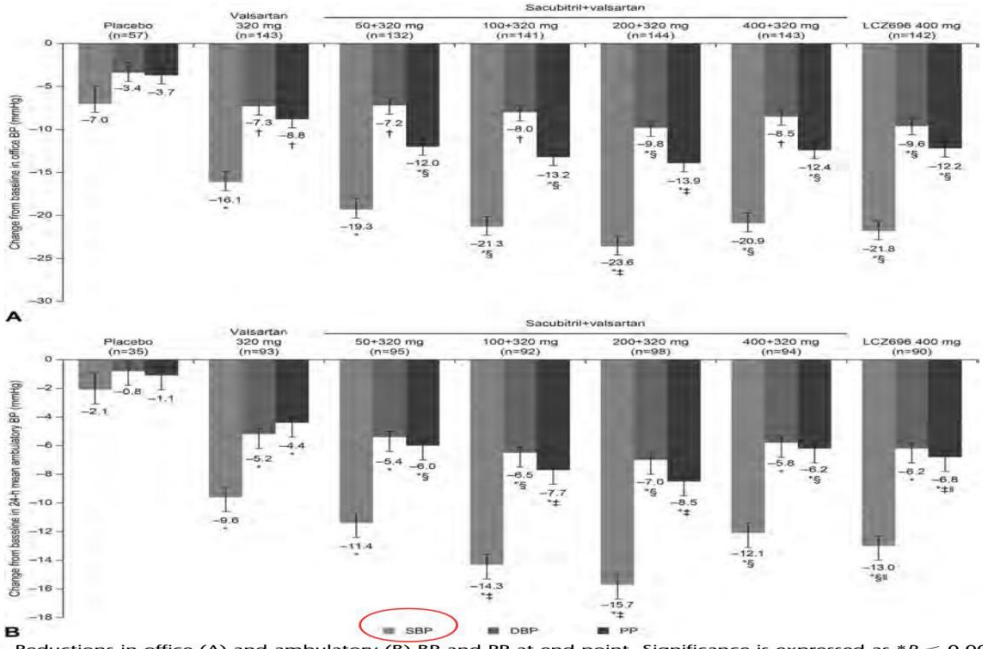


FIGURE 2. Reductions in office (A) and ambulatory (B) BP and PP at end point. Significance is expressed as $*P < 0.0001$ versus placebo, $\dagger P < 0.05$ versus placebo, $\ddagger P < 0.0001$ versus valsartan 320 mg, $\S P < 0.05$ versus valsartan 320 mg, and $\| P < 0.05$ versus sacubitril 200 mg + valsartan 320 mg. Bars represent standard error.

The opponent 2 further argued that **Izzo et al.** clearly states that **LCZ696 has similar efficacy to the combination of free valsartan 320 mg plus free sacubitril 200 mg** – *IN FACT FIGURE 2 SHOWS THAT THE REDUCTION ACHIEVED WITH THE COADMINSITRATION OF SACUBITRIL 200MG + VALSARTAN 320 MG IS BETTER THAN THAT OF LCZ696. Therefore, IZZO ET AL. FAILS TO ESTABLISH THAT THE EFFICACY OF LCZ696 IS SUPERIOR THAN THE PHARMACEUTICAL COMBINATION, WHICH IS DISCLOSED IN D1.*

The opponent 2 further submitted that " the Applicant deliberately avoids pointing out the following in the Figure which only **highlights no enhancement in efficacy –**

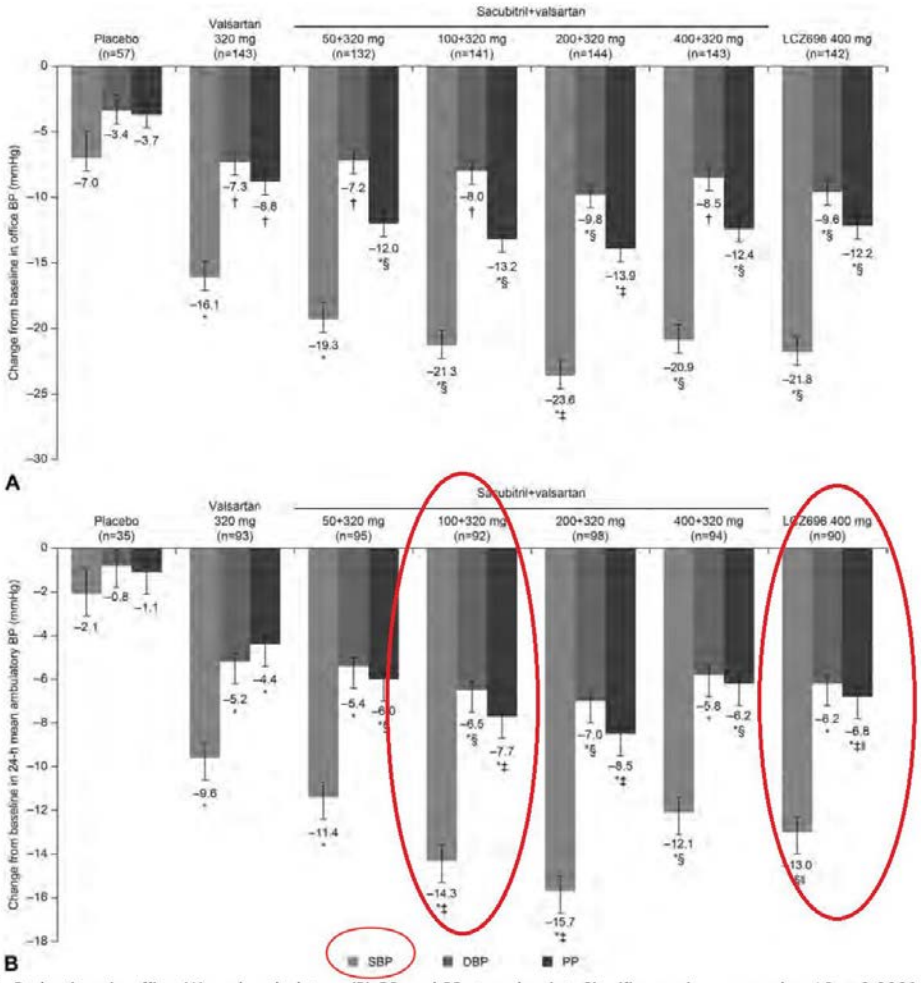


FIGURE 2. Reductions in office (A) and ambulatory (B) BP and PP at end point. Significance is expressed as $*P < 0.0001$ versus placebo, $\dagger P < 0.05$ versus placebo, $\ddagger P < 0.0001$ versus valsartan 320 mg, $\S P < 0.05$ versus valsartan 320 mg, and $\| P < 0.05$ versus sacubitril 200 mg + valsartan 320 mg. Bars represent standard error.

The opponent 2 discussed the data submitted by the Applicant with the Reply Statement by way of Annexure II. The Opponent states that firstly 5 the veracity of the data is questionable and cannot be relied on as the additional data was presented as a mere Annexure and not by way of an affidavit. The study provides results of a randomized, double blind, placebo-controlled, active comparator study.

Para 67 the opponent submitted that None of the other publications referred to by the Applicant's Expert evidence show unexpected benefits or properties.

Document	Opponent's remarks
Feng et al. LCZ696: a dual-acting sodium supramolecular complex	Reports the supramolecular structure of LCZ696
Gu et al : Pharmacokinetics and pharmacodynamics of LCZ696, a novel Dual Acting Angiotensin Receptor-Neprilysin Inhibitor (ARNi)	Compares LCZ696 with Valsartan and Sacubitril (AHU377) and not with a combination (As taught in D1)
Ruilope et al. Blood-pressure reduction with LCZ696, a novel dual-acting inhibitor of the angiotensin II receptor and neprilysin: a randomised, double-blind, placebo-controlled, active comparator study	Compared LCZ696 with valsartan (and NOT A COMBINATION OF VALSARTAN AND SACUBITRIL AS TAUGHT IN D1) and reports that it provides complementary and fully additive reduction of blood pressure, which suggests that the drug holds promise for treatment of hypertension and cardiovascular disease.
Mishra et al. - Management protocols for chronic heart failure in India	Does not contain any comparative data let alone It is a report on current management protocols for treatment of heart failure which report was been developed with an objective to provide standard management guidance and simple heart failure algorithms to aid Indian clinicians in their daily practice.

McMurray et al. - Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure	Compares compared the angiotensin receptor–neprilysin inhibitor LCZ696 with enalapril in patients who had heart failure with a reduced ejection fraction. In previous studies, enalapril improved survival in such patients. It is not proper to compare with a commercial alternative. Proper comparison in view of teachings of D1 would involve comparison with physical mixture showing unpredictable and unexpected benefits.

The opponent 2 further submitted that submitted that in light of above, the active ingredients were well known in their anionic forms at the time of the 5 invention (see D2 and D3). D1 discloses and teaches combined unit dose of Valsartan and Sacubitril was known at the time of the invention. The claimed compound being a supramolecular complex is nothing but a co-crystal. The Opponents submits that preparation of co-crystals of drug candidates were a well-known concept at the time of the invention. Therefore, in view of D1 and the common general knowledge a skilled person would have been able to arrive at the alleged invention as sought to be claimed. It would be but natural for a skilled person to prepare the combination in solid forms like crystals and co-crystals in order to achieve the expected and predicted physico-chemical properties. The Applicant failed to submit data which corroborates its stance that the alleged compound as claimed has UNEXPECTED BENEFITS, particularly in view of D1.

The opponent 2 submitted that a definitive expectation of success is not required in order to establish obvious, all that the Opponent is required to show is that there was a reasonable expectation of success of preparing a co-crystal and supramolecular complex of Valsartan and Sacubitril in order to achieve the desired properties.

The Opponent 2 further submitted that the requirement of inventive step under the Indian law is unique and unlike other jurisdictions, the test of inventive step is two pronged. Section 2(1)(ja) defines " inventive step" as a feature of an invention that involves technical advance as compared to the existing knowledge or having economic significance or both and that makes the invention not obvious to a person skilled in the art. Thus, an Applicant needs i) to demonstrate that there is technical advancement and that ii) and that technical advance is such that it make the invention not obvious to person skilled in the art. The requirement to satisfy both the limbs under the Indian Law aids in sieving trivial inventions from the more substantial ones. Accordingly, the claimed invention is obvious to a skilled person, as preparing the claimed supramolecular complex, in view of the teachings of D1 with common general knowledge in the art as documented in D4, D5 and D6 is routine experimentation. Even in the combined light of D1, D2 and D3 with the knowledge available to a skilled person, it would be obvious design and prepare a complex with to obtain better physico-chemical properties such as crystallinity, low hygroscopicity, stability, as it is devoid of any technical advance. It is submitted that the Applicant has merely conducted experiments in order to verify and validate expected findings. 20 Such routine experimentation, however much labourious and lengthy does not render an invention not obvious and technically advances compared to the existing knowledge.

It is further submitted that the commercial success of a drug is not an indicator of patentability. SUCH COMMERCIAL SUCCESS MAY BE A SECONDARY CONSIDERATION under the US law, however the impugned application being an Indian application shall be prosecuted as per the laws of the land where even the Intellectual Property Appellate Board has held it to be SECONDARY CONSIDERATIONS.

The Opponent 2 also refers to the Affidavit of Dr. Ramesh Dhandla filed on August 9,

2022 *(rebuttal evidence by the Opponent) in support of its case which specifically deals with the affidavits filed by the Applicant on June 6, 2020 and is not a mere denial as projected by the Applicant but in fact categorically explains the technical documents relied upon by the Applicant and its experts to show that the alleged invention claimed in the impugned patent application 4412/DELNP/2007 is obvious and devoid of inventive step.*

The Applicant had also referred to the following orders of the

Delhi High Court

a) ***Division Bench of the Delhi High 5 court in Roche v/s Cipla, RFA (OS)***

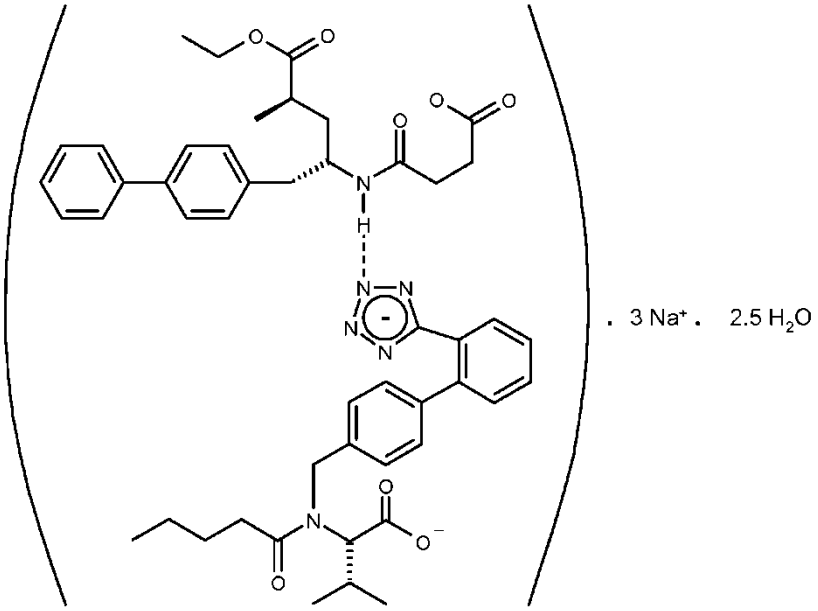
92/2012Para 57. *This argument ignores the fundamental truth about breakthrough inventions, which at the time they are invented may not be commercially the most viable for immediate marketing. They are useful and are industrially 10 applicable as without them there would be no stepping stone to achieve the next lot of improvements.*

b) ***Delhi High Court in BMS vs BDR, DHC, CS(COMM) 27/2020***

This Court has already noted that no drug came out of IN-917 and the first marketable drug came pursuant to the suit patent IN-381 which itself is sufficient to show enhanced efficacy'

The case laws under the ground of obviousness was shared vide email dated May 13, 2021 (on the date of the earlier hearing) and the submitted at the present hearing that the Opponent is relying on the same at the present hearing but not repeating to save time, wherein the operative portions are highlighted in yellow. For ready reference, said compilation is being annexed herewith as ANNEXURE B. In view of the above, the claims 1 to 8 of the impugned application ought to be rejected on this ground alone.

The applicant submitted that *the present invention is* ***the dual-acting compound, in particular the supramolecular complex is described by the sum formula:[((S)-N-valeryl-N-{[2'-(1H-tetrazole-5-yl)-biphenyl-4-yl]-methyl}-valine) ((2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester)]Na_3 • x H_2O****, wherein x is 0 to 3, such as 2.5. In this most preferredexample, the complex is termed trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate.A simplified structure of trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate used to formally calculate the relative molecular mass, is shown below*



Valsartan comprises two acidic groupings: the carboxylic acid and the tetrazole. In one embodiment of this aspect of the present invention, the molecular structure of the dual-acting compound, in particular, the complex, of valsartan and a NEPi comprises an interaction between the carboxylic acid and the cation, such as Na, or the solvent, such as water, or a linkage between the tetrazole grouping and the cation, such as Na, or the solvent, such as water. In yet another embodiment, the dual-acting compound, in particular, the complex, comprises an interaction between the valsartan carboxylic acid grouping, the tetrazole grouping or the NEPi grouping and the cation, such as Na, or the solvent, such as water.

The dual-acting compound, in particular, the complex, of the present invention is in the solid form. In the solid state it can be in the crystalline, partially crystalline, amorphous, or polymorphous form, preferably in the crystalline form. [0045] The dual-acting compound, in particular, the complex, of the present invention is distinct from a combination of an ARB and a NEPi obtained by simply physically mixing the two active agents. Thus, it can have different properties that make it particularly useful for manufacturing and therapeutic applications. The difference of the dual-acting com- pound, in particular, the complex, and the

combination can be exemplified by the dual-acting compound of (S)-N-valeryl- N-{[2'-(1H-tetrazole-5-yl)-biphenyl-4-yl]-methyl}-valine and (2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2- methyl-pentanoic acid ethyl ester which is characterized by very distinct spectral peaks and shifts that are not observe in the physical mixture.Specifically, such a dual-acting compound is preferably characterized by an X-ray powder diffraction patter

taken with a Scintag XDS2000 powder diffractometer using Cu-Ka radiation (lamda=1.54056 A) with a Peltier-coole Silicon detector at room temperature (25degree C). Scan range was from 1.5degree to 40degree in 2 theta with a sca rate of 3degree/minute. The most important reflections in the X-ray diffraction diagram comprise the following interlattice plane intervals:

SECTION 25(1)(f) : NOT AN INVENTION/NOT PATENTABLE :

Section 2(1)(ja)

The opponent no 2 (Natco Pharma) submitted that the claimed invention of the impugned application is not an invention under Section 2(1)(ja) as it is devoid of an inventive step for reasons stated in paragraphs under the preceding ground of obviousness/lack of inventive step. The submissions are not reiterated for the sake of brevity. It is stated that there is no technical advancement over the existing art or economic significance. Therefore, it is stated that the claims of the impugned application warrant rejection for failing to meet the Section 2(1)(j) and 2(1)(ja).

Section 3(d)

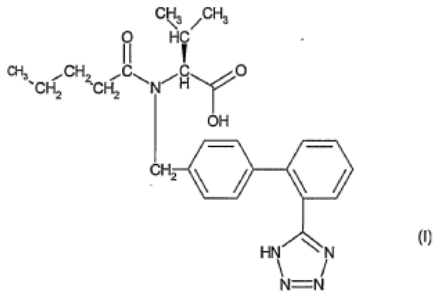
The opponent no 2 (Natco Pharma) submitted that the claimed compound is a new form of the pharmaceutical combinations comprising valsartan or pharmaceutically acceptable salts thereof and a neutral endopeptidase (NEP) inhibitor or a pharmaceutically effective salts thereof, taught in D1.

D1 at page 2 discloses that –

In one aspect the present invention relates to pharmaceutical combinations comprising valsartan or pharmaceutically acceptable salts thereof and a neutral endopeptidase (NEP) inhibitor or a pharmaceutically effective salts thereof, optionally in the presence of a pharmaceutically acceptable carrier and pharmaceutical compositions comprising them.

Further at page 3 , it discloses

Valsartan is the AT 1 receptor antagonist (S) -N-(1-carboxy-2-methyl-prop-1-yl)-pentanoyl-N-[2;(1 H-tetrazol-5-yl)biphenyl-4-yl-methyl]amine of formula (I) and disclosed in EP 0443983 A and United States Patent 5,399,578, the disclosures of



(I)

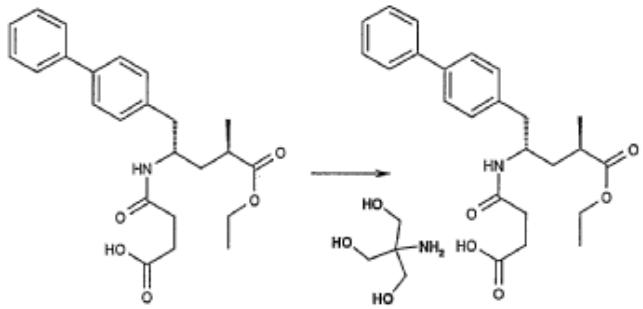
which are incorporated herein in their entirety as if set forth herein.

Further at pages 6 and 7, D1 discloses,

The compounds to be combined can be present as pharmaceutically acceptable salts. If these compounds have, for example, at least one basic center, they can form acid addition salts. Corresponding acid addition salts can also be formed having, if desired, an additionally present basic center. The compounds having at least one acid group (for example COOH) can also form salts with bases. Corresponding internal salts may furthermore be formed, if a compound comprises e.g. both a carboxy and an amino group.

With respect to N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4- amino-2R-methylbutanoic acid ethyl ester, preferred salts include the

sodium salt disclosed in U.S. Patent No. 5,217,996, the triethanolamine salt and the tris(hydroxymethyl)aminomethane salt.



The salts of N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester formed with triethanolamine and tris(hydroxymethyl) aminomethane are novel and can be used as NEP inhibitors.

At pages 7 and 8, D1 discloses:

It has surprisingly been found that, a combination of valsartan and a NEP inhibitor achieves greater therapeutic effect than the administration of valsartan, ACE inhibitors or NEP inhibitors alone and promotes less angioedema than is seen with the administration of a vasopeptidase inhibitor alone. Greater efficacy can also be documented as a prolonged duration of action. The duration of action can be monitored as either the time to return to baseline prior to the next dose or as the area under the curve (AUC) and is expressed as the product of the change in blood pressure in millimeters of mercury (change in mmHg) and the duration of the effect (minutes, hours or days). [page 7 of D1]

At page 9, D1 discloses a person skilled in the pertinent art is fully enabled to select a relevant test model to prove the efficacy of a combination of the present invention in the hereinbefore and hereinafter indicated therapeutic indications. It further provides representative studies with a combination of valsartan and N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester (Sacubitril). Following the DOCA-salt test, the efficacy of the combination was assessed.

Further benefits are that lower doses of the individual drugs to be combined according to the present invention can be used to reduce the dosage, for example, that the dosages need not only often be smaller but are also applied less frequently, or can be used to diminish the incidence of side effects. The combined administration of valsartan or a pharmaceutically acceptable salt thereof and a NEP inhibitor or a pharmaceutically acceptable salt thereof results in a significant response in a greater percentage of treated patients, that is, a greater responder rate results, regardless of the underlying etiology of the condition. This is in accordance with the desires and requirements of the patients to be treated.
It can be shown that combination therapy with valsartan and a NEP inhibitor results in a more effective antihypertensive therapy (whether for malignant, essential, reno-vascular, diabetic, isolated systolic, or other secondary type of hypertension) through improved efficacy as well as a greater responder rate. The combination is also useful in the treatment or prevention of heart failure such as (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter or detrimental vascular remodeling

The available results indicate an unexpected therapeutic effect of a combination according to the invention. [page 12 of D1] In this composition, components (i) and (ii) can be obtained and administered together, one after the other or separately in one combined unit dose form or in two separate unit dose forms. The unit dose form may also be a fixed combination. [page 13 of D1]

A therapeutically effective amount of each of the component of the combination of the present invention may be administered simultaneously or sequentially and in any order. D1

also discloses and teaches the dose at which valsartan and sacubitril are administered.

Valsartan is supplied in the form of suitable dosage unit form, for example, a capsule or tablet, and comprising a therapeutically effective amount, e.g. from about 20 to about 320 mg, of valsartan which may be applied to patients. The application of the active ingredient may occur up to three times a day, starting e.g. with a daily dose of 20 mg or 40 mg of valsartan, increasing via 80 mg daily and further to 160 mg daily up to 320 mg daily. *Preferably, valsartan is applied once a day or twice a day in heart failure patients with a dose of 80 mg or 160 mg, respectively, each. Corresponding doses may be taken, for example, in the morning, at mid-day or in the evening. Preferred is q.d. or b.i.d. administration in heart failure.*

In case of NEP inhibitors, preferred dosage unit forms are, for example, tablets or capsules comprising e.g. from about 20 mg to about 800 mg, preferably from about 50 mg to about 700 mg, even more preferably from about 100 mg to about 600 mg and even more preferably from about 100 mg to about 300 mg, administered once a day.

The opponent no 2 (Natco Pharma) submitted In summation, **D1 discloses**

- *PHARMACEUTICAL COMBINATIONS comprising VALSARTAN or pharmaceutically acceptable salts thereof and SACUBITRIL or a pharmaceutically effective salts thereof, optionally in the presence of a pharmaceutically acceptable carrier and pharmaceutical compositions comprising them.*

- *VALSARTAN and SACUBITRIL administered together, one after the other or separately in ONE COMBINED UNIT DOSE FORM or in two separate unit dose forms. The unit dose form may also BE A FIXED COMBINATION. [page 13 of D1]*

- *VALSARTAN AND SACUBITRIL IN COMBINATION*

- *results indicate AN UNEXPECTED THERAPEUTIC EFFECT Of a combination according to the invention.*

- *achieves GREATER THERAPEUTIC EFFECT THAN THE ADMINISTRATION OF VALSARTAN, ACE INHIBITORS OR NEP INHIBITORS ALONE and promotes less angioedema than is seen with the administration of a vasopeptidase inhibitor alone.*

- *GREATER EFFICACY can also be documented as A Prolonged Duration Of Action.*

- *LOWER DOSES OF THE INDIVIDUAL DRUGS TO BE COMBINED according to the present invention can be used to REDUCE THE DOSAGE, for example, that the dosages need not only often be smaller but are also applied less frequently, or can be USED TO DIMINISH THE INCIDENCE OF SIDE EFFECTS.*

- *Results in a MORE EFFECTIVE ANTIHYPERTENSIVE THERAPY THROUGH IMPROVED EFFICACY AS WELL AS A GREATER RESPONDER RATE.*

- *useful in the TREATMENT OR PREVENTION OF HEART FAILURE SUCH AS (ACUTE AND CHRONIC) CONGESTIVE HEART FAILURE, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter or detrimental vascular remodeling.*

The opponent no 2 (Natco Pharma) submitted that the claimed compound being a supramolecular complex of the combination taught in D1 squarely attracts Section 3(d).

- **The KNOWN SUBSTANCE - pharmaceutical combinations in form of one combined unit dose form of valsartan and sacubitril**

- **the NEW FORM - supramolecular complex (also known as a co-crystal) of valsartan and sacubitril along with sodium (cation) and water**

To qualify as patentable subject matter under Section 3(d) the new form ought to have shown **ENHANCED EFFICACY over the known substance.**

Pare 80 in the reply the opponent argued that One combined unit dose of Valsartan and Sacubitril was known at the time of the invention. The claimed compound being a supramolecular complex is nothing but a co- crystal. The Opponents submits that preparation of co-crystals of drug candidates were a well-known concept at the time of the invention.

Without prejudice to the objections filed in respect of the filing of the Expert Affidavits which incidentally are dated before the Form-13 dated June 6, 2020 under Section 57, **the Opponent 2** would like to refer to the expert affidavits to demonstrate that the claimed compound is admittedly a co-crystal form of a known combination.

Dr. Karpinski in the prosecution of the corresponding **US patent, US8877938,**
83.

1) Item 4 of the Karpinski declaration states:

Under my direction and supervision, working diligently, over 1000 separate experiments were initially required to prepare, purify and characterize substantially pure trisodium [3-((1 S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate. The procedure to prepare, purify and characterize this compound was non-routine and required an undue level of experimentation. Many of the compounds which were isolated in the experiments were not sufficiently stable to be characterized and as such, they were considered poor candidates for further development.

The opponent no 2 (Natco Pharma) submitted that, the Applicant during the Indian prosecution on May 30, 2016 deleted the claims directed to such crystalline form in order to overcome the objection under Section 3(d) , which claims were also annexed to the reply statement of the Applicant dated March 3, 2017, thus admitting that the said fails attracted Section 3(d). The Ld. Controller during the proceedings on May 13, 2021, indicated that he did not direct such amendments. Thus, such amendments were with an intent to mislead and hoodwink the Ld. Controller to avoid the requirement of demonstrating enhanced therapeutic efficacy, which is a requirement under Section 3(d) of the Indian law.

Thus, inspite of the compound being a crystalline, single compound, the Applicant sought to evade such inquiry under Section 3(d) by deleting the claims reciting that the compound is crystalline is nature.

The opponent no 2 (Natco Pharma) submitted that Even the affidavits of ***Dr. Allan S. Myerson and Dr. Gauri Billa*** *reinforces that the claimed compound is nothing but a crystalline form of a known combination. It is submitted that the claimed compound, particularly LCZ696 is a co-crystal.*

The opponent 7 (Chirag Tanna) submitted *that* the specification and the claims relate to a supramolecular complex. It is admitted by the Applicant that there is a prior art **WO2003059345,** which discloses a physical mixture of Valsartan and Sacubitril.

The technical effect of the supramolecular complex of the invention is nothing but preparation of a molecular assembly in which sodium ions together with Valsartan, Sacubitril and water ions co-exist and are bound by inter- molecular bonds. It is well known that a technical effect must be shown in the specification as of the date of filing. The specification does not describe or enable a person skilled in the art as to whether the description is complete and specifically does not state the technical effect.

The technical effect is the heart beat of the invention as it demonstrates the alleged infringement or efficacy of the complex. However, there is no such example in the entire specification, much less any data.

The opponent 7 (Chirag Tanna) submitted that Through the affidavit of Dr. Motto (para 23), there is an attempt to show that the supramolecular complex has a faster dissolution rate as compared to the physical mixture of Valsartan and Sacubitril. None of this features in the application as filed – hence all of this cannot now be considered for purposes of section 3(d) assessment.

The opponent 7 (Chirag Tanna) submitted a careful observation of the table shown therein would illustrate that the time (about 180 minutes) taken for dissolution of entire quantity of the physical mixture and of the supramolecular complex is the same, and the percentage of the drug released (at pH 6.8) is also the same. To elaborate, at pH 6.8, the amount of valsartan released is same as LCZ696 VAL. This means that the efficacy of both is equivalent. Also, in the dissolution graphs at pH 4.5 and 6.8, the release of valsartan is shown to be more than 100%, which is not possible. Dr Motto, in his affidavit at para 20, states that the supramolecular complex has improved stability as compared to the physical mixture. It is well known that mere bioavailability does not amount to therapeutic effect (Novartis Vs. Union of India, para 189).

The opponent 7 (Chirag Tanna) submitted that the Applicant has placed reliance on the post-published article Izzo et al. (published in 2017) to demonstrate the alleged enhanced effectiveness of LCZ696 compared to effectiveness of valsartan monotherapy alone in lowering BP in patients with systolic hypertension (see Izzo et al., conclusion, internal page 380). However, in the study upon which the said article is based, the amount of LCZ696 dosed was 400 mg while the

amount of valsartan dosed was 320 mg across all cohorts studied. It is submitted that the same dose of valsartan and sacubitril should have been administered in the study to all study participants in said study. Moreover there is no rationale provided in the article as to why the dose strength of LCZ696 and valsartan that had been administered is not identical. It is humbly submitted that in order to adjudge the enhanced therapeutic efficacy, it is important to administer an equal dosage of compounds being studied because an unequal amount of dosage will result in different plasma concentrations and levels of the compounds in the body and hence, it will be impossible to ascertain enhanced therapeutic efficacy. Due to the above, it is not possible to draw any meaningful conclusions regarding therapeutic efficacy from the study and the same should be disregarded. With regard to the post-published disclosure relied upon by the Applicant for demonstrating enhanced dissolution of supramolecular complex (in the Motto affidavit) and Izzo et al. (demonstrating comparative data on blood pressure reduction), reliance is placed on the judgment of **Honourable High Court of Delhi in ASTRAZENECA AB & ANR versus INTAS PHARMACEUTICALS LIMITED (CS (COMM) No. 410/2020**)

The case pertained to the compound Dapagliflozin where the application did not show synergistic effect in specification as filed.

The judgment at para 29.2 to para 30 elucidate the following:

First part involves patentee to show that the invention claimed in any claim involves "technical advance" as compared to the existing knowledge or has "economic significance" or both. The second part of the definition alludes to the fact that the invention should not be obvious to the person skilled in the art.

The plaintiffs sought to get over this by seeking to rely upon **Dr. Washburn's affidavit of April 2020** which was filed on 12.10.2020 to show technical advance. The data pertaining to technical advance is set out in **Dr. Washburn's affidavit under the following broad headings.**

"**A**. Enhanced selectivity for SGLT2 versus SGLT1

B. Enhanced ability to reduce blood glucose at 5 hours after oral administration to diabetic STZ rats (short-term animal model)

C. Enhanced ability to reduce plasma glucose over a 15- day period after oral administration to ZDF rats (longer- term animal model)"Based on the data set out in the affidavit, **Dr. Washburn** made the following conclusions.

In my opinion, the increased selectivity and the reduction of glucose levels obtained with dapagliflozin compared to Example 12 of WO '128 in the STZ and ZDF rat models were surprising and unexpected.

In my opinion, the glucose reductions in STZ and ZDF rats are particularly surprising considering that, in the in vitro experiments, the SGLT2 inhibitory potential (EC50) of dapagliflozin was seemingly similar to the SGLT2 inhibitory potential of Example 12 of WO '128."

In my opinion, if this information was not available at the time the application for grant of patent was filed, then, this cannot be taken into account, at this juncture, by the plaintiffs in support of their plea that IN 625 involved an inventive step. There is no clue in IN 625 of an unknown technical effect on its priority date. Dr. Washburn's affidavit, who professes to be the co-inventor of DAPA, could have come to the rescue of the plaintiffs to demonstrate technical advance if, at least a seed of that nature had been planted in IN 625, on its priority date.

The Applicant has argued that once the product is marketed, there is no need to demonstrate any efficacy and reliance was placed on the judgment of BMS v BDR.

The opponent 7 (Chirag Tanna) submitted that the Applicant is selectively reading para 45 of the said judgment. The said judgment has to be seen in the context of the whole case. In that case (BMS v BDR), the plaintiff had already proved efficacy in the specification. Hence the court held that the product was marketed and therefore no further proof of efficacy is required. This judgment is not to be read as if no proof of efficacy is required at all once the product is marketed. The judgment does not give an avenue to bypass the provisions of section 3(d).

The opponent no 7 argued that**, the claims are not patentable under Section 3(d) of the Act and liable to be rejected for lack of therapeutic efficacy.**

The opponent no 8 (Dr. Ketakee Durve) submitted that the subject invention of claim 1 is hit by the 1st exclusion contained in S. 3(d), i.e., the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance.

The opponent no 8 (Dr. Ketakee Durve) submitted that the "known substance" is valsartan+sacubitril. It is submitted that the "known efficacy" of said "known substance" is its use as antihypertensive drug.

The opponent no 8 (Dr. Ketakee Durve) submitted that a complex of this known substance will amount to a "new form" since the explanation to S. 3(d) expressly lists "complexes" of known substances. Accordingly, a prima facie case is made out under S. 3(d), and the burden shifts to the patent applicant to demonstrate a "significant" enhancement in efficacy. In this context, efficacy means actual therapeutic efficacy, i.e., the ability to cure the underlying disease or condition, and not mere bioavailability increase or advantages in physical properties that don't translate to efficacy. Reference in this regard may be had to pages 89-91 of the Manual for Patent Office Practice and Procedure dated 26.11.2019 citing the judgement of the Hon'ble Supreme Court in Novartis AG v. Union of India [W.P. No. 24760/06]. A copy of this was handed over during the hearing and enclosed herewith for completeness of record. However, the complete specification fails in this respect because there is absolutely no detail or explanation on how the complex results in enhancement in therapeutic efficacy, let alone a significant enhancement.

The opponent no 8 (Dr. Ketakee Durve) submitted that that the applicant tries to overcome this fatal lacuna by emphasising on an article called "Izzo et al.". However, this attempted reliance on "Izzo et al." cannot save the patent applicant for the following reasons:

a) First, this is a document that is outside the four corners of the complete specification. More importantly, to the best of the knowledge of the Opponent, this is a post-priority document published in June 2017. It is now a settled proposition of law that post-priority publications cannot be used as evidence unless the specification plausibly reflects such data or information. Reliance in this regard may be placed on Astrazeneca AB & Anr. v. Intas Pharmaceutical Ltd. (supra) [@ paras 30 & 30.3], previously referred to, which read as follows:

30. In my opinion, if this information was not available at the time the application for grant of patent was filed, then, this cannot be taken into account, at this juncture, by the plaintiffs in support of their plea that IN 625 involved an inventive step. There is no clue in IN 625 of an unknown technical effect on its priority date. Dr. Washburn's affidavit, who professes to be the co-inventor of DAPA, could have come to the rescue of the plaintiffs to demonstrate technical advance if, at least a seed of that nature had been planted in IN 625, on its priority date. ...

30.3 On behalf of Generics, it was contended that the claimed inventions made no technical contribution to the art and, therefore, did not involve inventive steps as summarized in another judgement i.e. Generics (UK) Ltd vs Yeda Research and Development Co Ltd, [2013] EWCA Civ 925 Alternatively, it was argued that the technical contribution was insufficient as per principles summarised by Kitchin LJ in Idenix Pharmaceuticals Inc vs. Gilead Sciences Inc, [2016] EWCA Civ 1089. The Court after discussing the issue made the following crucial observations.

197. In case this case goes further, I must briefly address the Defendants' reliance upon evidence which post-dates the priority date of the Patent. It is common ground that such evidence can only be relied upon to confirm the existence of a technical effect which is plausible in the light of the specification and the skilled person's common general knowledge, and not to establish the existence of a technical effect for the first time.

The opponent no 8 (Dr. Ketakee Durve) submitted that in the oral hearing, applicant tried to show that the specification of the impugned application contained a "seed" of the alleged enhanced properties of the supramolecular complex by relying on pages 8-11, 24 and 14 29 of the complete specifications. In reality, all these references only state that the supramolecular complex has "distinct" properties from that of the earlier known combination. Stating that something is "distinct" does not mean it has enhanced properties; by plain English, this different is clear.

Morevoer, the test as per Astrazeneca AB & Anr. v. Intas Pharmaceutical Ltd. (supra) [@ para 30.3] is that the specification must plausibly state such enhanced properties, i.e., it must be plausible to the person skilled in the art. This is not fulfilled in this case.

(c) In the oral hearing, applicant also tried to argue that the above proposition is only for inventive step and not Section 3(d). This is not an acceptable argument because patent validity is always assessed on priority date; it is a fundamentally cut-off point and thus, the propostion logically extends to Section 3(d) also. **The opponent no 8 argued** that the applicant kept repeating that the rules and the guidelines permitted such post-filing data, no such rule or guideline was actually shown during the hearing.
(d)Second, it is not as if the patent applicant does not know how such enhanced efficacy can be shown. D1A, their own prior patent for the combination of the same two active ingredients, refers to increased efficacy and studies to prove the same (internal page 8, para 2; internal pages 9 and 11). But no such references are seen in the impugned application.
(e) Third, even assuming without conceding that said "Izzo et al." is to be considered, page 24, para 78 of the patent applicant's reply to the opposition shows that there is no "significant" difference in the efficacy between sacubitril+valsartan (D1A) versus sacubitril and valsartan in a complex (impugned application)

The opponent no 8 (Dr. Ketakee Durve) submitted that that It is essential to keep in mind the object and purpose of S. 3(d) when considering the facts of the present case. The Supreme Court has recognised that it is to prevent evergreening and the grant of successive monopolies on pharmaceutical substances/products by making insignificant changes. This is precisely what the patent applicant is attempting here. From D1A, combining valsartan and sacubitril in their salt forms was already known. Said D1A also expressly taught that administering them together as a combination resulted in enhancement of efficacy. At best, taking the most favourable position for the patent applicant, the present invention merely changes the mode of delivery, i.e., instead of using two chemical compounds in one physical carrier, the two chemical compounds are combined in a complex form. Ultimately, in vivo, the 15 two active ingredients will separate from the complex and independently act to their respective modes of action.
The opponent no 8 argued that the present invention is merely a change in the mode of deployment of the active ingredients and nothing more. Such patents are certainly not intended to pass the threshold under S. 3(d).

Applicant Arguments and Submission Section 3(d)

The applicant submitted that the Opponent NO 8 at the hearing with regard to Section 3(d) made the following contention.
a) Valsartan + Sacubitril combination is known substance from D1, WO '345
b) Ajanta vs Allergan, IPAB order is not applicable in instant case
c) There is no enhancement of efficacy when the combination of Valsartan and Sacubitril is compared with LCZ696
d) Comparison made by Dr Gauri Billa is irrelevant

The applicant submitted that the patent specification, the present invention is directed to a unique and novel dual-acting compound that has also been defined on *pages 9 and 10 of the patent*

specification. The claimed compound is a unique and novel compound (or supramolecular complex), which comprises
a) **anionic** Valsartan,
b) **anionic** Sacubitril, and
c) **sodium cations** at a molar ratio of 1:1:3.
d) The compound may further contain water molecules, and has a hydration state defined in the claims by "x", which is 0-3 in claim 1, such as 0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 1, 2.25, 2.5, 2.75, or 3 (*p. 22 second to last paragraph and p. 23*).

The applicant submitted that the patent specification as well as in paras 16 to 19 above, the present invention is directed to a unique and novel dual-acting compound that has also been defined on *pages 9 and 10 of the patent specification.* The claimed compound is a unique and novel compound (or supramolecular complex), which comprises

a) **anionic** Valsartan,

b) **anionic** Sacubitril, and

c) **sodium cations** at a molar ratio of 1:1:3.

d) The compound may further contain water molecules and has a hydration state defined in the claims by "x", which is 0-3 in claim 1, such as 0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 1, 2.25, 2.5, 2.75, or 3 (*p. 22 second to last paragraph and p. 23*).

e) The compound is stabilized by non-covalent interactions (including hydrogen bonds, ionic bonds and van der Waals forces).

The applicant argued that NOVEL compound claimed in claim 1 is a 'trisodium-Sacubitril-Valsartan' compound (and may also include water molecules) and is **not** a **new form** of **a** known substance nor is merely a salt of Sacubitril or salt of Valsartan. The claims of the present invention are directed to a **new compound / a new dual acting compound** wherein the angiotensin receptor blocker (ARB) and neutral endopeptidase inhibitor (NEPI) having different modes of action are linked by non-covalent bonding in **one compound.**

The novel compound of the present invention is not a new form of the combination of Valsartan and Sacubitril disclosed in WO 345 for the purpose of Section 3(d) of the Indian Patents Act.

The claimed supramolecular compound is unique and is different from a physical mixture of Valsartan and Sacubitril. The XRD, solid state NMR, DSC, SEM, ATR-FTIR data confirm the unique feature of LCZ696, which is a representative compound of claim 1.

The applicant argued that present claimed **novel and unique compound** is not a physical mixture of individual Na salts of Valsartan and Sacubitril but a compound that exhibited

distinctly different spectral features in comparison to 1:1 mixture of the sodium salt ***(page 46, para 3 of the patent specification*)**.

The applicant further argued , Dr. Myerson also in paras 2.1 to 2.10 of his affidavit refers to the present invention as a "new / novel compound". Dr. Motto also in his affidavit at para 19 and 22, refers to the present invention as being "a single compound". Also, experts of reputed scientific publications, for example *Feng et al* refer to LCZ696 as a potentially **promising novel active ingredient** in pharmaceutical products.

(B) The claimed compound of IN '4412 is neither a complex or combination for purposes of Section 3(d) in view of Allergan vs Ajanta, IPAB order

The applicant further submitted that the claimed compound (or supramolecular compound) does not fall under the definition 'complex' or combination mentioned in the explanation part of Section 3(d). In this regard, reference has been made to the *Allergan vs Ajanta, IPAB, order 172/2013.*

a) The alleged patent in the Allergan vs Ajanta, IPAB case, IN219504, was in relation to composition / combination comprising two active ingredients 'Brimonidine and Timolol' for treatment of glaucoma. Claim 1 of IN219504: "*An Ophthalmic pharmaceutical composition useful in the treatment of glaucoma or ocular hypertension comprising a concentration of 0.01 to 0.5 per cent by weight of Brimonidine and a concentration of 0.1 to 1.0 per cent by weight of timolol in pharmaceutically acceptable carrier therefor*."

b) **IPAB Finding**: Combination of two actives do not fall under the explanation part of Section 3(d).

Para 84: The explanation to the section enumerates various derivatives of the known substance *which shall be considered to be the same substance unless, there is significantly different in therapeutic efficacy. Therefore, all the forms of the known substance that are mentioned are derivatives of the known substance which could be salts, esters, ethers and so on.* ***" … [The combination mentioned in the Explanation can be only mean a combination of two or more of the derivatives mentioned in the Explanation*** *or combination of one or more of the derivatives with the known substance which may result in a significant difference with regard to the efficacy. A combination of two active drugs like Brimonidine and Timolol cannot be considered derivatives of each other.* ***This ground is rejected.***

Thus, **combination under Section 3(d) means "Combination of a salt/ether/ derivative/ new form** etc of Valsartan or Sacubitril in view of Allergan case of IPAB.

10.10 The term "combination" as appearing in Section 3(d) has been explained by IPAB as "The combination mentioned in the Explanation can only mean a combination of two or more of the derivatives mentioned in the Explanation or combination of one or more of the derivatives with the known substance which may result in a significant difference with regard to the efficacy"[19].

[19]Ajantha Pharma Limited Vs Allergan Inc. and Others,ORA/21/2011/PT/KOL of Order no. 173 of 2013, Paragraph 84

Patent Office incorporated this case in the "Guidelines for Examination of Patent Applications in the Field of Pharmaceuticals" [para 10.10] for interpreting the term "combination" as appearing in Section 3(d).

'Complex' *is also a generic expression which means that the complex should include a derivative of a known substance.*

Patents granted for complex: *This is clearly established by at least 2 cases granted by the Indian Patent Office where Section 3(d) was not an issue which was a complex of a single active ingredient and a co-former agent. The grant of these patents without a 3(d) objection clearly establishes complex under Section 3(d) needs to have at least a single ingredient which has to necessarily be a derivative of the known substance for instance a complex of a polymorph of rivaroxaban or etravirine: which means that there should be one API..*

a**) 8827/DELNP/2010** (Indian patent No. 280026) co-crystal of rivaroxaban and malonic acid

b) **2132/MUMNP/2011** (Indian Patent No. 327493)-co crystal of etravirine and nicotinamide (co-crystal former).

The applicant submitted that the applicant in their patent specification has defined "supramolecularcomplex" as an interaction between the two pharmaceutically active agents, cations and any other entity present by means of non-covalent intermolecular bonding between them *(page 10 last para of the patent specification)* and is not the complex as stated in Section 3(d).

(C) No 'known substance with known efficacy' known at the priority date for the purpose of Section 3(d)

In the present case, firstly, there is no known substance. The novel supramolecular compound was not known at the priority date.

a) The compound is not a new form (for example a new polymorph or a new hydrate) of a previously known compound – it is a new, single compound per se, having a completely new structure.

b) As on the priority date of the present application for the purpose of Section 3(d):

1) Valsartan was a known substance with known efficacy. Valsartan has known efficacy by virtue of its approval as a marketable drug DIOVAN *(Annexure 2 of Dr. Myerson's affidavit)* in 1996

2**) Sacubitril was a known substance but did not have any known efficacy. It is submitted that Sacubitril efficacy for Section 3(d) was not disclosed in US5217996 nor was Sacubitril approved as a monotherapy drug. Sacubitril was approved as a drug only with the commercial product that came out of IN 4412, i.e. Entresto® is the first and only regulatory approval of Sacubitril. In other words, Sacubitril has not been approved till date as a monotherapy and was approved for the first time in Entresto®.**

3) **The combination of Sacubitril and Valsartan as disclosed in WO 2003/059345 is not the known substance with known efficacy for Section 3(d) on at least two accounts:**

i. That Section 3(d) requires "A" known substance and therefore a combination of Sacubitril and Valsartan (i.e 2 actives) cannot be "A" known substance under Section 3(d) or be considered a known substance in view of the IPAB order in *Ajanta vs Allergan*.

In view of the above, the 'trisodium Sacubitril and Valsartan complex' cannot be considered as the same substance of the "known substance" having "known efficacy" of either Valsartan or Sacubitril.

It is for the first time that two active ingredients have been combined in a unique and novel and inventive compound having a specific structure and comprises anionic Valsartan, anionic Sacubitril, and sodium cations at a molar ratio of 1:1:3, optionally with water molecules.

IZZO CONFIRMS EFFICACY AND SAFETY OF LCZ696 IN THE RATIO STUDY:

The applicant argued that the authors of the Izzo article were able to compare **Sacubitril and**

Valsartan with LCZ696 and draw conclusions about their therapeutic efficacies**.**

a) Izzo et al article titled "*Efficacy and Safety of Crystalline Valsartan/Sacubitril (LCZ696) Compared with Placebo and Combinations of Free Valsartan and Sacubitril in Patients with Systolic Hypertension: The RATIO Study*" Relates to clinical trial studies of the commercial product LCZ 696.

b) The only "known substance" with "known efficacy" under Section 3(d) as on the priority date of the IN' 4412 application is **Valsartan free acid**, which was the only approved form of Valsartan sold under the brand name of Diovan and Co-Diovan.

c) At the priority date of the application, while Sacubitril was a known substance, it did not have any known efficacy as required by Section 3(d) as Sacubitril was not approved in any form or for any indication.

> 5.2 Neprilysin, a neutral endopeptidase, degrades several endogenous vasoactive peptides, including natriuretic peptides, bradykinin, and adrenomedullin. Inhibition of neprilysin increases the levels of these substances, countering the neuro-hormonal over-activation that contributes to vasoconstriction, sodium retention, and maladaptive remodelling. LCZ696, which consists of the neprilysin inhibitor sacubitril (AHU377) and the ARB valsartan, acts by dual action – i.e. inhibition of RAAS system by an ARB (Valsartan) and upregulation of the Natriuretic Peptide (NP) system by inhibition of Neprilysin (sacubitril). LCZ696 is the first drug approved for the management of HFrEF that includes both an ARB and NEPi. LCZ696 is also the first (and only) regulatory approval of sacubitril. And, as of today, sacubitril remains the only approved NEP inhibitor.

d) Sacubitril was approved for the first time in LCZ696 and in this regard reference is made to para 5.2 of the affidavit of Dr. Gauri Billa that clearly states as follows:

It is important to note that in the studies carried out by Izzo et. Al., Valsartan was given as the maximumtherapeuticdose and therefore a dose beyond 320 mg of Valsartan is not permissible. In adult hypertension, Valsartan can only be used over a dose range of 80 mg to 320 mg daily, administered once a day.

From the abstract of the Izzo article itself, it is clear that the focus of the clinical trials was to compare the systolic blood pressure (SBP), lowering efficacy and safety of LCZ696

against Valsartan 320mg once daily alone or co-administered with placebo or increasing doses of Sacubitril (50, 100, 200, or 400 mg once daily). Under the head abstract, the studies clearly recognize the following:

a) That 400 mg of trisodium compound of Valsartan (206mg) and Sacubitril (194 mg)
mg

i. Is superior to Valsartan 320 mg of Valsartan for lowering systolic blood pressure;

ii. has similar efficacy to the combination of free Valsartan 320 mg + Sacubitril 200 mg;

iii. Represents optimal dosage for systolic hypertension and;

iv. Is safe and well tolerated.

Figure 2 relied upon by the Applicant from the Izzo article as shown herein below clearly establishes the aforesaid.

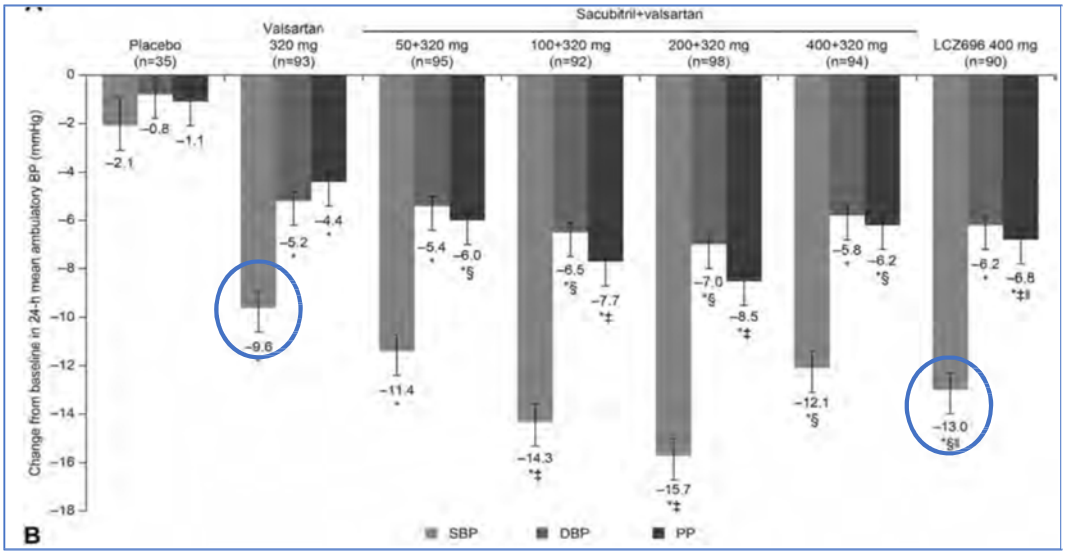


Figure 2: Reduction in blood pressure

	SBP	DBP	PP
Valsartan (320mg)	**-9.6**	**-5.2**	**-4.4**
Sacubitril + Valsartan (400 +320 mg)	**-12.1**	**-5.8**	**-6.2**
LCZ696 (400mg)	**-13.0**	**-6.2**	**-6.8**

Izzo article at page 380, states the following:
Thus:

a) Under the head "DISCUSSION" concludes that LCZ696 400 mg is superior to monotherapy Valsartan 320 mg for lowering systolic blood pressure (53.5 % vs 39.9 %)

b) LCZ696 was not associated with an increased prevalence of adverse events either in patients with hypertension and therefore the results show that the similar safety and tolerability profile of LCZ 696 was observed.

a) similar efficacy is achieved with lower amount of Valsartan in LCZ696 namely, 206 mg of Valsartan from LCZ696 versus 320 mg of Valsartan in the co- administered free combination (ca. 37% less).

b) despite lower dosage of the active Valsartan and similar dosage of the active Sacubitril, LCZ696 showed superior reductions from baseline in the mean sitting diastolic and systolic blood pressures compared to Valsartan alone.

The Applicant also at the hearing referred to Dr. Gauri Billa's affidavit, wherein the Applicant clearly demonstrated:

a) That the **standard of care** of at least two decades for treatment of heart conditions was Enalapril;

b) That LCZ696 after its approval is a **breakthrough product** and **class 1** recommendation for patient for HF with reduced ejection fraction (HFrEF);

c) That LCZ 696 has been held to be **superior** to the standard of care (ACE inhibitor Enalaprill for the treatment of HFrEF).

(E) RUILOPE COMPARES EFFICACY OF LCZ696 WITH VALSARTAN & SACUBITRIL

LCZ696 was tested in 1328 patients and was compared with Valsartan for reduction in blood pressure published by Ruilope et al., 2010.

a) Ruilope authors, compared with 200 mg Sacubitril and 320mg Valsartan, 400 mg LCZ696 (containing the equivalent amounts of 206 mg Valsartan and 194 mg Sacubitril) showed full additivity for reduction of mean sitting diastolic

blood pressure, and more than full additivity for reduction of mean sitting systolic blood pressure underscoring the complementary effects of the dual mechanism of action.

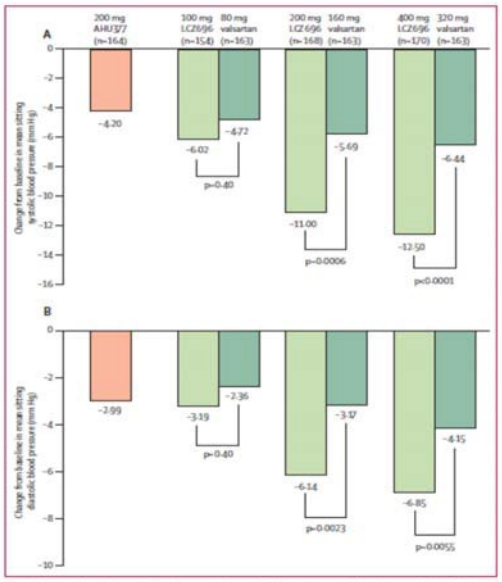


Figure 2: Change in placebo-subtracted mean sitting systolic blood pressure (A) and mean sitting diastolic blood pressure (B) during the 8-week treatment period
Patients who discontinued the study drug without a blood pressure measurement after randomisation were excluded.

b) From the compared dosages, namely 200 mg Sacubitril and 320 mg Valsartan which were compared with 400 mg LCZ696 (containing the equivalent amounts of 206 mg Valsartan and 194 mg Sacubitril); i.e., the amount of Valsartan in LCZ696 is significantly lower (206 mg) than the amount needed when administered in the free acid form (320 mg).

(F) <u>CONCLUSION ON SECTION 3(d)</u>

Applicant submitted that Section 3(d) is not applicable as the compound claimed in IN '4412 is a new compound wherein two active moieties Valsartan and Sacubitril are linked together through non-covalent interactions (hydrogen bonds, ionic and van der Waals forces).

a) The claimed compound of the IN' 4412 application is a **<u>new and unique single</u> <u>compound</u>** and is not a new form (not a polymorph, salt, complex or combination of a known substance.)

b) The claimed compound (or supramolecular compound) of the IN '4412 application does not fall under the definition of 'Complex' or combination' mentioned in the Explanation part of the Section 3(d).

c) There is no "known substance" with "known efficacy" according to Section 3(d). Sacubitril was not approved at the priority date.

d) The Izzo et al article clearly demonstrates that LCZ696 is far superior to the known drug Valsartan 320 mg and is well tolerated.

e) Furthermore, LCZ696 show enhanced efficacy over Valsartan and improvement over the physical combination of Valsartan and Sacubitril.

f) Reference is made to the order of Delhi High Court in BMS vs BDR, DHC, CS(COMM) 27/2020, enclosed as ***<u>Annexure 21</u>***. ***45. This Court has already noted that no***

drug came out of IN-917 and the first marketable drug came pursuant to the suit patent IN-381 which itself is sufficient to show enhanced efficacy.

In view of the Delhi High Court order in BMS vs BDR, a commercial marketable drug came pursuant to IN '4412 which is evidence of enhanced efficacy, thus the commercial product LCZ 696 /ENTRESTO involves research of at least two inventions namely IN229051 and IN '4412.

Applicant submitted that D4 (Morissette et al.) describes designing and preparing alternative crystalline forms like co- crystals where the convention crystal forms fails to have the desired effect. It discloses that it is a natural endeavour in pharmaceutical sciences to prepare solid forms as they provide many advantages (pg. 276). Similarly,

D5 (Almarsson et al.) discusses the evolution of crystal engineering into a form of supramolecular synthesis and the problems and opportunities in the pharmaceutical industry. It defines pharmaceutical co-crystals as being a subset of a broader group of multi-component crystals that also includes salts, solvates (pseudopolymorphs), clathrates, inclusion crystals and hydrates. In a supramolecular context, solvates and pharmaceutical co-crystals are related to one another in that at least two components of the crystal interact by hydrogen bonding and, possibly, other non-covalent interactions rather than by ion-pairing. Page 1894 (pg 236 of REP).

D6 (Vishweshwar et al.) discloses that Pharmaceutical co-crystals address physical property issues.

Submission and arguments on Efficacy

The Applicant in the Reply Statement dated March 3, 2017 states that D1 discloses a physical combination as opposed to a compound which is linked via non-covalent bonding. The Applicant contends that the claimed compound being a complex comprising two active ingredients do not fall within the scope of Section 3(d) and has referred to IPAB order in the matter of Allergan vs Ajanta.

The Opponent 2 Natco Pharma submittted that the facts of the matter in Allergan vs Ajanta was wholly different. The claimed combination therein was a physical mixture and not a complex and there was no disclosure or teaching in prior art to combine such actives in one combined unit dose form.

The Opponent 2 Natco Pharma submittted that the order of the Supreme Court has clearly observed that *This leaves us with the beta crystal form of Imatinib Mesylate, which, for the sake of argument, may be accepted to be new, in the sense that it is not known from the Zimmermann patent. (Whether or not it involves an "inventive step" is another matter, and there is no need to go into that aspect of the matter now). Now, the beta crystalline form of Imatinib Mesylate being a pharmaceutical substance and moreover a polymorph of Imatinib Mesylate, it directly runs into section 3(d) of the Act with the explanation appended to the provision. Mr. Subramanium, however, contended that section 3(d) has no application in this case. The main ground on which he denied the applicability of section 3(d) to decide the question of grant of patent to the beta crystalline form of the Imatinib Mesylate is earlier held to be untenable. He, however, questioned the applicability of section 3(d) on another ground.* ***Mr. Subramanium submitted that in order to attract section 3(d), the subject product must be a new form of a known substance having known efficacy.*** *The learned counsel laid some stress on the expression "known" that equally qualifies the substance of which the subject product may be another form, and the efficacy of that substance.* ***The learned counsel submitted that a "conceivable" substance is not a "known***

substance" within the meaning of the provision. He contended that the word "known" here connotes proven and well-established; "known efficacy" implies efficacy established empirically and proven beyond doubt. He further contended that neither Imatinib nor Imatinib Mesylate had any known efficacy and that, therefore, there was no question of showing that the beta crystalline form of Imatinib Mesylate had any enhanced efficacy *over Imatinib or Imatinib Mesylate.*

There is no sanction to construe the expression "known" in section 3(d) in the manner suggested by Mr. Subramanium, and the submission is unacceptable both in law and on facts. It may be noted here that clauses (e) and (f) of section 64(1) of the Act, which contain two of the grounds for revocation of patents, also use the expression "publicly known". The expression "publicly known" may normally be construed more widely than "known", and in that sense it is closer to the submission made by Mr. Subramanium. But even the expression "publicly known" received quite the opposite interpretation by this Court in Monsanto Company v. Coramandal Indag Products (P) Ltd.

In paragraph 6 of the judgment, Justice Chinnappa Reddy, speaking for the Court, held and observed as under:

"…To satisfy the requirement of being publicly known as used in clauses (e) and (f) of Section 64(1), it is not necessary that it should be widely used to the knowledge of the consumer public. It is sufficient if it is known to the persons who are engaged in the pursuit of knowledge of the patented product or process either as men of science or men of commerce or consumers. The section of the public, who, as men of science or men of commerce, were interested in knowing about Herbicides which would destroy weeds but not rice, must have been aware of the discovery of Butachlor. There was no secret about the active agent Butachlor as claimed by the plaintiffs since there was no patent for Butachlor, as admitted by the plaintiffs. Emulsification was the well-known and common process by which any herbicide could be used. Neither Butachlor no the process of emulsification was capable of being claimed by the plaintiff as their exclusive property. The solvent and the emulsifier were not secrets and they were admittedly not secrets and they were ordinary market products. From the beginning to the end, there was no secret and there was no invention by the plaintiffs. The ingredients, the active ingredients the solvent and the emulsifier, were known; the process was known, the product was known and the use was known. The plaintiffs were merely camouflaging a substance whose discovery was known through out the world and trying to enfold it in their specification relating to Patent Number 125381. The patent is, therefore, liable to be revoked.

On facts also we are unable to accept that Imatinib Mesylate or even Imatinib was not a known substance with known efficacy. It is seen above that Imatinib Mesylate was a known substance from the Zimmermann patent.

Therefore, **The Opponent 2 Natco Pharma submittted** that the Applicant"s arguments that a "conceivable" substance is not a "known substance" was dismissed by the Supreme Court. Therefore, the one combined unit dose form of D1

having established unexpected therapeutic efficacy was a known substance with a known efficacy at the time of the alleged invention.

Further reference is made to paragraphs
That being the position, the appellant was obliged to show the enhanced efficacy of the beta crystalline form of Imatinib Mesylate over Imatinib Mesylate (non-crystalline). *There is, however, no material in the subject application or in the supporting affidavits to make any comparison of efficacy, or even solubility, between the beta crystalline form of Imatinib Mesylate and Imatinib Mesylate (noncrystalline)*

. As regards the averments made in the two affidavits, for all one knows the higher solubility that is attributed to the beta crystalline form of Imatinib Mesylate may actually be a property of Imatinib Mesylate itself. ***One does not have to be an expert in chemistry to know that salts normally have much better solubility than compounds in free base form. If that be so, the additional properties that may be attributed to the beta crystalline form of Imatinib Mesylate would be limited to the following:***

i. More beneficial flow properties,
ii. Better thermodynamic stability, and
iii. Lower hygroscopicity

The aforesaid properties, ("physical attributes" according to Manley), would give the subject product improved processability and better and longer storability but, as we shall see presently, on the basis of those properties alone, the beta crystalline form of Imatinib Mesylate certainly cannot be said to possess enhanced efficacy over Imatinib Mesylate, the known substance immediately preceding it, within the meaning of section 3(d) of the Act.

*We have so far considered the issue of enhanced efficacy of the subject product inlight of the finding recorded earlier in this Judgment that Imatinib Mesylate (noncrystalline) is a known substance from the Zimmermann patent and is also the substance immediately preceding the patent product, that is****, Imatinib Mesylate in beta crystallineform.***

What is "efficacy"? Efficacy means "the ability to produce a desired or intended result". Hence, the test of efficacy in the context of section 3(d) would be different, depending upon the result the product under consideration is desired or intended to produce. In other words, the test of efficacy would depend upon the function, utility or the purpose of the product under consideration. Therefore, in the case of a medicine that claims to cure a disease, the test of efficacy can only be "therapeutic efficacy". The question then arises, what would be the parameter of therapeutic efficacy and what are the advantages and benefits that may be taken into account for determining the enhancement of therapeutic efficacy? With regard to the genesis of section 3(d), and more particularly the circumstances in which section 3(d) was amended to make it even more constrictive than before, we have no doubt that the "therapeutic efficacy" of a medicine must be judged strictly and narrowly

Our inference that the test of enhanced efficacy in case of chemical substances, especially medicine, should receive a narrow and strict interpretation is based not only on external factors but there are sufficient internal evidence that leads to the same view. It may be noted that the text added to section 3(d) by the 2005 amendment lays down the condition of "enhancement of the known efficacy". Further, the explanation requires the derivative to "differ significantly in properties with regard to efficacy". What is evident, therefore, is that not all advantageous or beneficial properties are relevant, but only such properties that directly relate to efficacy, which in case of medicine, as seen above, is its therapeutic efficacy.

. While dealing with the explanation it must also be kept in mind that each of the different forms mentioned in the explanation have some properties inherent to that form, e. g., solubility to a salt and hygroscopicity to a polymorph. These forms, unless they differ significantly in property with regard to efficacy, are expressly excluded from the definition of "invention". Hence, the mere change of form with properties inherent to that form would not qualify as "enhancement of efficacy" of a known substance. In other words, the explanation is meant to indicate what is not to be considered as therapeutic efficacy.

In whatever way therapeutic efficacy may be interpreted, this much is absolutely clear: that the physico-chemical properties of beta crystalline form of Imatinib Mesylate, namely (i) more beneficial flow properties, (ii) better thermodynamic stability, and (iii) lower hygroscopicity, may be otherwise beneficial but these properties cannot even be taken into account for the purpose of the test of section 3(d) of the Act, since these properties have nothing to do with therapeutic efficacy.

This leaves us to consider the issue of increased bioavailability. It is the case of the appellant that the beta crystalline form of Imatinib Mesylate has 30 per cent increased bioavailability as compared to Imatinib in free base form. If the submission of Mr. Grover is to be accepted, then bioavailability also falls outside the area of efficacy in case of a medicine. Leaving aside the submission of Mr. Grover on the issue, however, the question is, can a bald assertion in regard to increased bioavailability lead to an inference of enhanced therapeutic efficacy? Prof. Basheer quoted from a commentator on the issue of bioavailability as under: ***"It is not the intent of a bio-availability study to demonstrate effectiveness, but to determine the rate and extent of absorption. If a drug product is not bioavailable, it cannot be regarded as effective. However a determination that a drug product is bio-available is not in itself a determination of effectiveness."***

Thus, even if Mr. Grover's submission is not taken into consideration on the question of bioavailability, the position that emerges is that just increased bioavailability alone may not necessarily lead to an enhancement of therapeutic efficacy. ***Whether or not an increase in bioavailability leads to an enhancement of therapeutic efficacy in any given case must be specifically claimed and established by research data. In this case, there is absolutely nothing on this score apart from the adroit submissions of the counsel. No material has been offered to indicate that the beta crystalline form of Imatinib Mesylate will produce an enhanced or superior efficacy (therapeutic) on molecular basis than what could be achieved with Imatinib free base in vivo animal model.***

Pare 93 the opponent 2 argued that the expert evidence of Dr Gauri Billa, the Opponent submits that event though Dr. Gauri Billa‟s affidavit dated JUNE 5, 2020 is on Section 3(d) , she does not even whisper on D1, leave alone commenting on how the claimed compound is not a mere discovery of the new form of a known substance.

As stated in paragraph 2 of the affidavit, her opinion as an expert in the field of Pharmacology is on the fact as to whether Vymada, which contains LCZ696 as the active substance, is a novel therapeutic option in the treatment of Heart Failure with reduced ejection fraction, and if so, why?

In doing so, she has relied upon studies which compare LCZ696/Vymada (the tradename under which the product is marketed) with existing therapies with Enalapril and arrives at the finding that the claimed compound has purported therapeutic efficacy which was hitherto unknown.

Much statements were also made on that Sacubitril was never approved or developed as a drug.it is submitted said argument has no relevance in terms of the Indian patent Law as "known" is not necessarily restricted to commercially known.

Even though Dr. Gauri Billa‟s affidavit is on Section 3(d), the Applicant did not rely on her affidavit at the hearing, which clearly go to show that the comparison based on which Dr. Billa

has arrived at the finding of therapeutic efficacy of LCZ696 is not proper and fair insofar as the Indian patent law, specifically Section 3(d) is considered.

The opponent 2 Natco Pharma submitted that in view of D1, the Applicant ought to have provided comparative data with a physical mixture, at the least, to establish enhanced therapeutic efficacy. The Applicant placed reliance on Izzo et al. , annexure to Dr. Allan S. Myerson, which is a 2017 publication on "Efficacy and Safety of Crystalline Valsartan/Sacubitril (LCZ696) Compared With Placebo and Combinations of Free Valsartan and Sacubitril in Patients With Systolic Hypertension: The RATIO Study"

Izzo et al. compared the systolic blood pressure (SBP)- lowering efficacy and safety of crystalline valsartan/sacubitril (LCZ696, an angiotensin receptor blocker–neprilysin inhibitor) 400 mg daily against valsartan (320 mg once daily) alone or coadministered with placebo or increasing doses of free sacubitril (50, 100, 200, or 400 mg once daily) to identify the optimal antihypertensive combination dose. **It further states that the SBP reduction with LCZ696 400 daily was similar to coadministered free valsartan 320 mg and sacubitril 200 mg.** Effects were similar in those older and younger than 65 years, and active therapies had adverse event rates similar to placebo. Izzo et al. concludes that crystalline valsartan/sacubitril 400 mg daily (1) is superior to valsartan 320 mg daily for lowering SBP, (2) **has similar efficacy to the combination of free valsartan 320 mg plus free sacubitril 200 mg,** (3) represents the optimal dosage for systolic hypertension in patients of any age, and (4) is safe and well tolerated.

The opponent 2 Natco Pharma submitted that Izzo et al. fails to substantiate the contentions of the Applicant under Section 3(d). Izzo et al. concludes that crystalline valsartan/sacubitril 400 mg daily (1) is superior to valsartan 320 mg daily (i.e. valsartan separately) for lowering SBP – THAT THE COMBINATION WAS SUPERIOR TO VALSARTAN PER SE WAS KNOWN AT THE TIME OF THE INVENTION FROM THE DISCLOSURE OF D1.

The Opponent 2 refers **to Figure 2 in Izzo et al.**

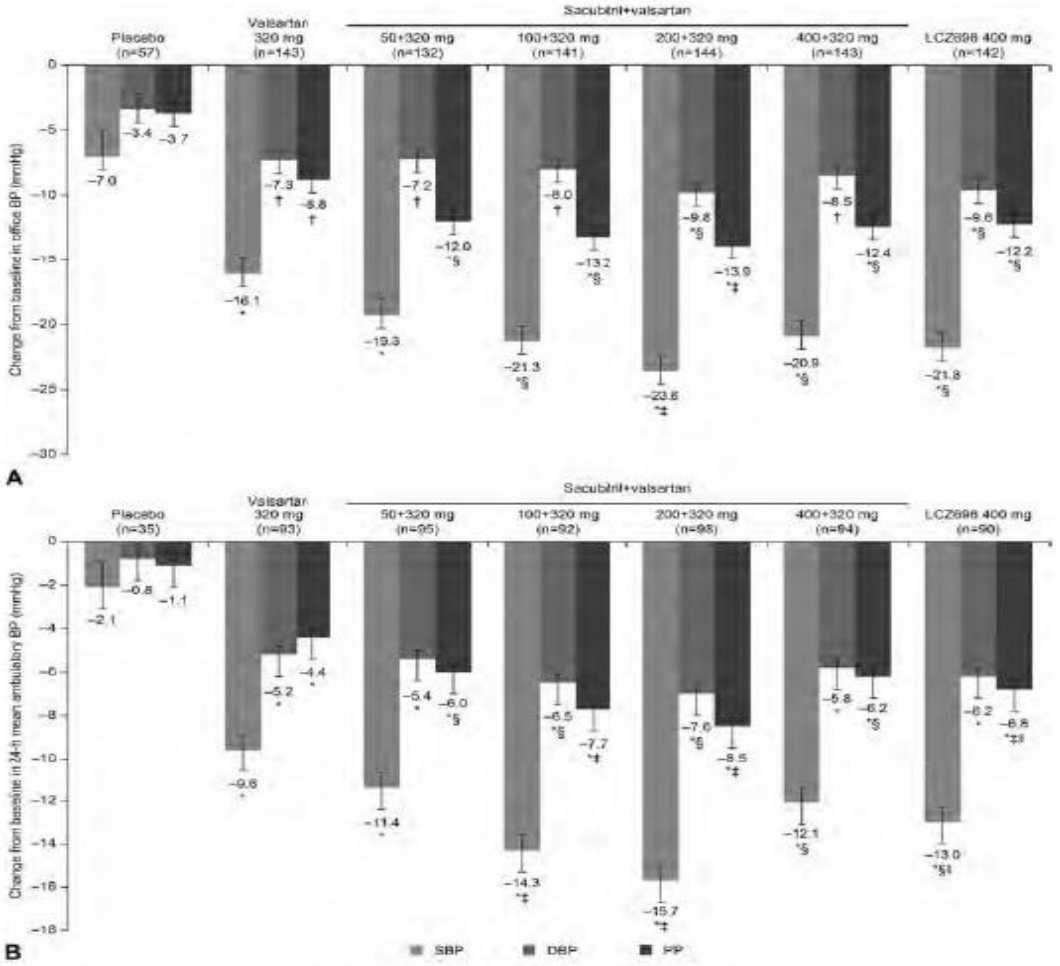


FIGURE 2. Reductions in office (A) and ambulatory (B) BP and PP at end point. Significance is expressed as $*P < 0.0001$ versus placebo, $\dagger P < 0.05$ versus placebo, $\ddagger P < 0.0001$ versus valsartan 320 mg, $\S P < 0.05$ versus valsartan 320 mg, and $\| P < 0.05$ versus sacubitril 200 mg + valsartan 320 mg. Bars represent standard error.

The opponent 2 Natco Pharma submitted that Izzo et al. clearly states that LCZ696 has similar efficacy to the combination of free valsartan 320 mg plus free sacubitril 200 mg – IN FACT FIGURE 2 SHOWS THAT THE REDUCTION ACHIEVED WITH THE COADMINSITRATION OF SACUBITRIL 200MG + VALSARTAN 320 MG IS BETTER THAN THAT OF LCZ696. Therefore, IZZO ET AL. FAILS TO ESTABLISH THAT THE EFFICACY OF LCZ696 IS SUPERIOR THAN THE PHARMACEUTICAL COMBINATION, WHICH IS DISCLOSED IN D1. Even the data submitted by the Applicant with the Reply Statement dated March 3, 2017 by way of Annexure II. **The Opponent states** that firstly the veracity of the data is questionable as the additional data was presented as a mere Annexure and not by way of an affidavit. The study provides results of a randomized, double blind, placebo-controlled , active comparator study.

The INTERPRETATION as provided at page 43 states

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Compared with valsartan, dual-acting LCZ696 provides complementary and fully additive reduction of blood pressure, which suggests that tlie drug holds promise for treatment of hypertension and cardiovascular disease.

The opponent 2 Natco Pharma submitted submitted that when two drugs with different mechanism of action are combined, they are expected to have additive effect. In the present case, D1 already established that the combination (even as a ONE COMBINED UNIT DOSE FORM) has an unexpected therapeutic efficacy. Therefore, the present invention provides a new supramolecular form (co-crystal) which has expected benefits of stability.
The Applicant in the Reply Statement further states that a fixed 1:1 molar ratio of Sacubitril to Valsartan is provided and simplification due to dealing with one single material in the compounding and manufacturing of the drug product; and better physical properties for material handling (less hygroscopic, better solubility). It is submitted such advantages are inherent to co-crystals as taught in D4 to D6 and is not unexpected. Moreover in view of D1, it was incumbent on the Applicant to demonstrate enhanced efficacy by way of additional data.

The opponent 2 Natco Pharma submitted that such additional data and the data provided by way of Izzo et al. therefore proves that the Opponent˝s contention that the claimed compound fails to provide any enhanced therapeutic efficacy over the pharmaceutical combinations disclosed and taught in D1. Accordingly, in absence of enhanced therapeutic efficacy the subject matter of impugned application is not patentable under Section 3(d).

It is thus submitted that the claimed invention squarely attracts Section 3(d) and the Applicant has miserably failed to demonstrate any therapeutic efficacy as required under Section 3(d). The impugned application ought to be rejected on this ground alone.

Applicant Submission on Efficacy

<u>The applicant submitted that Izzo confirms Efficacy and Safety of LCZ696 in The RATIO Study:</u>

The applicant submitted that **the argument of the Opponent (*<u>para 39 to 42 of Dr Ramesh Dandala affidavit</u>*) appears to be far-fetched**. It is clear that the authors of the Izzo article were able to compare **Sacubitril and Valsartan with LCZ696** and draw conclusions about their therapeutic efficacies**.**
a) **Izzo et al article titled** "*Efficacy and Safety of Crystalline Valsartan/Sacubitril (LCZ696) Compared with Placebo and Combinations of Free Valsartan and Sacubitril in Patients with Systolic Hypertension: The RATIO Study*" Relates to clinical trial studies of the commercial product LCZ 696.
b) The only "known substance" with "known efficacy" under Section 3(d) as on the priority date of the IN' 4412 application is **Valsartan free acid**, which was the only approved form of Valsartan sold under the brand name of Diovan and Co-Diovan.

c) At the priority date of the application, while Sacubitril was a known substance, it did not have any known efficacy as required by Section 3(d) as Sacubitril was not approved in any form or for any indication.

d) **Sacubitril was approved for the first time in LCZ696 and in this regard reference is made to para 5.2 of the affidavit of Dr. Gauri Billa** that clearly states as follows:

5.2	Neprilysin, a neutral endopeptidase, degrades several endogenous vasoactive peptides, including natriuretic peptides, bradykinin, and adrenomedullin. Inhibition of neprilysin increases the levels of these substances, countering the neuro-hormonal over-activation that contributes to vasoconstriction, sodium retention, and maladaptive remodelling. LCZ696, which consists of the neprilysin inhibitor sacubitril (AHU377) and the ARB valsartan, acts by dual action – i.e. inhibition of RAAS system by an ARB (Valsartan) and upregulation of the Natriuretic Peptide (NP) system by inhibition of Neprilysin (sacubitril). LCZ696 is the first drug approved for the management of HFrEF that includes both an ARB and NEPi. LCZ696 is also the first (and only) regulatory approval of sacubitril. And, as of today, sacubitril remains the only approved NEP inhibitor.

The applicant submitted it is important to note that in the studies carried out by Izzo et. Al., Valsartan was given as the maximumtherapeuticdose and therefore a dose beyond 320 mg of Valsartan is not permissible. In adult hypertension, Valsartan can only be used over a dose range of 80 mg to 320 mg daily, administered once a day. From the abstract of the Izzo article itself, it is clear that the focus of the clinical trials was to compare the systolic blood pressure (SBP), lowering efficacy and safety of

The applicant submitted LCZ696 against Valsartan 320mg once daily alone or co-administered with placebo or increasing doses of Sacubitril (50, 100, 200, or 400 mg once daily). Under the head abstract, the studies clearly recognize the following:

a) That 400 mg of trisodium compound of Valsartan (206mg) and Sacubitril (194 mg) mg

i. Is superior to Valsartan 320 mg of Valsartan for lowering systolic blood pressure;

ii. has similar efficacy to the combination of free Valsartan 320 mg + Sacubitril 200 mg;

iii. Represents optimal dosage for systolic hypertension and;

iv. Is safe and well tolerated.

Figure 2 relied upon by the Applicant from **the Izzo article** as shown herein below clearly establishes the aforesaid.

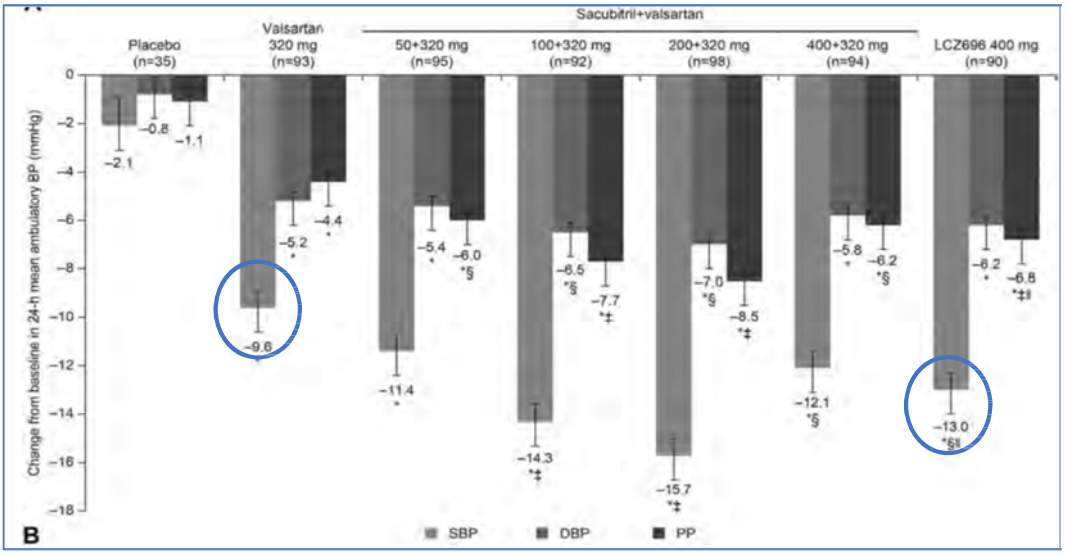


Figure 2: Reduction in blood pressure

	SBP	DBP	PP
Valsartan (320mg)	**-9.6**	**-5.2**	**-4.4**
Sacubitril + Valsartan (400 +320 mg)	**-12.1**	**-5.8**	**-6.2**
LCZ696 (400mg)	**-13.0**	**-6.2**	**-6.8**

The applicant submitted Izzo article at page 380, states the following:

a) Under the head "DISCUSSION" concludes that LCZ696 400 mg is superior to monotherapy Valsartan 320 mg for lowering systolic blood pressure (53.5 % vs39.9 %)

b) LCZ696 was not associated with an increased prevalence of adverse events either in patients with hypertension and therefore the results show that the similar safety and tolerability profile of LCZ 696 was observed. Thus:

a) similar efficacy is achieved with lower amount of Valsartan in LCZ696 namely,
206 mg of Valsartan from LCZ696 versus 320 mg of Valsartan in the co- administered free combination (ca. 37% less).

b) despite lower dosage of the active Valsartan and similar dosage of the active Sacubitril, LCZ696 showed superior reductions from baseline in the mean sitting diastolic and systolic blood pressures compared to Valsartan alone.

The Applicant also at the hearing referred to Dr. Gauri Billa's affidavit, wherein the Applicant clearly demonstrated:

a) That the **standard of care** of at least two decades for treatment of heart conditions was Enalapril;

b) That LCZ696 after its approval is a **breakthrough product** and **class 1** recommendation for patient for HF with reduced ejection fraction (HFrEF);

c) That LCZ 696 has been held to be **superior** to the standard of care (ACE inhibitor Enalaprill for the treatment of HFrEF).

(E) Ruilope compares efficacy of LCZ696 with Valsartan & Sacubitril

LCZ696 was tested in 1328 patients and was compared with Valsartan for reduction in blood pressure published by Ruilope et al., 2010.

a) Ruilope authors, compared with 200 mg Sacubitril and 320mg Valsartan, 400 mg LCZ696 (containing the equivalent amounts of 206 mg Valsartan and 194 mg Sacubitril) showed full additivity for reduction of mean sitting diastolic blood pressure, and more than full additivity for reduction of mean sitting systolic blood pressure underscoring the complementary effects of the dual mechanism of action.

b) From the compared dosages, namely 200 mg Sacubitril and 320 mg Valsartan which were compared with 400 mg LCZ696 (containing the equivalent amounts of 206 mg Valsartan and 194 mg Sacubitril); i.e., the amount of Valsartan in LCZ696 is significantly lower (206 mg) than the amount needed when administered in the free acid form (320 mg).

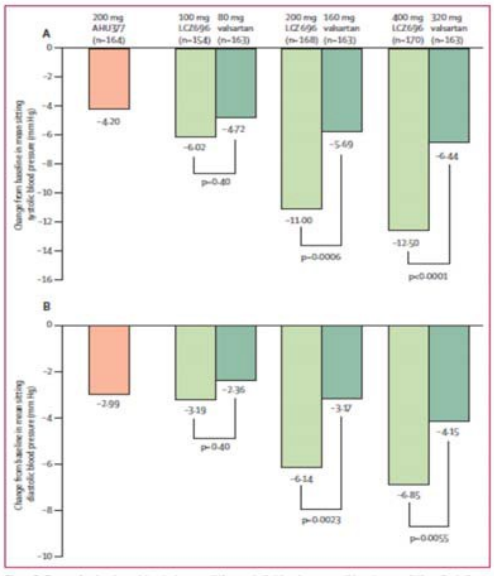


Figure 2: Change in placebo-subtracted mean sitting systolic blood pressure (A) and mean sitting diastolic blood pressure (B) during the 8-week treatment period
Patients who discontinued the study drug without a blood pressure measurement after randomisation were excluded.

SECTION 25(1)(G): INSUFFICIENT DISCLOSURE

The Opponent 2 submitted that the complete specification of the alleged invention does not sufficiently and clearly describe the claimed invention. The Opponent states that it is a well settled rule that the specification should clearly and fairly describe the invention and disclose the best mode of working the invention so that the person skilled in the art could perform the invention without any undue efforts and it is hereby stated that the Applicant has failed to do so. The claims are unduly broad and claimed compounds of valsartan and sacubitril may have 0 to 3 degrees of hydration. Even though the applicant has claimed several hydrate forms in the claims, the specification only describes the preparation of only the hemipentahydrate form. It is stated that the applicant has claimed a range of molecular forms such as a hydrate, hemihydrate, monohydrate, sesquihydrate, dehydrate and trihydrate. Claim 1 on record encompasses several forms of the dual-acting compound, but the impugned specification does not sufficiently disclose the method of preparation ofall those compounds and the reaction conditions whereby all of the compounds of claim 1 may be prepared, except that for hemi- pentahydrate form. In absence of such preparation methods a person of average skill has to conduct undue experimentation in order to formulate such crystalline and salt forms. There is no example or description which would enable preparation of a supramolecular complex when x is = 0 i.e. the anhydrate form (without water). Examples 1 to 3 of the impugned application relate to the hemipentahydrate form, that is a compound where x is = 2.5.

The opponent 2 further submitted that In fact in the Reply Statement dated March 3, 2017 the Applicant has categorically stated t importance of the water molecules for the HIGHLY INTRICATE SUPRAMOLECULA STRUCTURE that –

8. It is submitted that the claimed compounds are unique compounds wherein the two anionic components (Valsartan and Sacubitril) together with sodium cations and water molecules are linked together with non-covalent bonds to form a single large and highly intricate supramolecular structure. None of the prior art documents cited by the Opponent disclose or suggest a supramolecular compound as claimed in the present application and, as such, these documents cannot

Thus, when x is = 0 i.e. the anhydrate form (without water) is impossible according to the Applicant itself. In fact the expert affidavits filed by the Applicant on June 6, 2020 highlight this fact.

In this context, it is significant to have in mind that the Dr. Peter Karpinski (the inventor) in his declaration in the USPTO, clearly state that the other forms were undesirable and poor candidates. He further states that 1000 separate experiments were initially required to prepare, purify and characterize the claimed compound. It is thus submitted that a skilled person would require undue experimentation to prepare the prepare the other hydrate and anhydrate forms other than hemipentahydrate.

The opponent 2 argued that the Applicant is clearly trying to re-claim the combination in a surreptitious manner by making misleading statements since according to its own statement, in absence of water the HIGHLY INTRICATE SUPRAMOLECULAR STRUCTURE will not form.

The aforesaid fact is also evident from all major jurisdictions and the reference to the EP divisional **EP 2340828 B1** by the Applicant is totally misleading since the same relates admittedly to a different invention (which also includes mixtures) from the specific hemipentahydrate (wherein x is 2.5) crystalline form. The Applicant made such statement during prosecution of the said divisional at the EPO. The Applicant seeks to make gross misrepresentations before the Indian Patent Office.

The Opponent 2 also relies on the Affidavit of Dr. Ramesh Dhandla filed on 15 August 9, 2022 which highlights the insufficiency of the broad scope of the invention? which lacks support in the specification.

The opponent 2 submitted that the below case laws were relied upon by the Applicant **(portions as reproduced in the slides of the Applicant handed out at the hearing are Reproduced below),** –

.

1) Specification is addressed to a person skilled in the art (POSA). *Para 14 in F.H. v. Unichem, [AIR 1969, Bom 255 14]*

2) Example do not limit the scope of the claimed invention in any manner and are merely added to enable the skilled person to perform the claimed invention without any undue experimentation. *In Re Specialty Composites, 845 F.2d 981*

3) The examples provided in the specification are sufficient enough to enable the skilled person to perform the claimed invention in its entire scope and that claims are sufficiently clear, without any ambiguity. *Charles R. Christianson V Colt Industries Operating Corp.[822 F.2d 1544]*

4) Claims and specification should be read as a whole to assess claims for insufficiency. *Para 44 in Bishwanath Prasad vs Hindustan Metal, (1979) 2 SCC 511.*

5) Claims should be read in conjunction with the description. *Roche vs CIPLA, RFA 92/2021, DHC, 2015, para 34 .*

6) Claim scope need not be the same in all jurisdiction. *CCA Inc vs Ace Technology DHC, CS (Comm) 1222/2018, para 41*

7) **Guidelines for the examination of Patent Applications in the field of pharmaceuticals on page 39, para 11:**
"....The description in the specification should contain at least one example or more than one example, covering the full breadth of the invention as claimed, which enable(s) the person skilled in the art to carry out the invention".

8) **FDC vs Sanjeev Khandelwal, order dated 21st March 2014, IPAB held as follows:**
"114. As per sec 10(4), every complete *specification shall fully and particularly describe the invention and disclose the best method of performing the invention which is known to the applicant. However, it is not mandatory that the claims should be representative of the best method" Thus, the IPAB has indicated that the sufficiency of disclosure requirement is met if at least one way of working the invention is clearly indicated enabling the skilled person to carry out the*

9) **Tata Global Beverages Limited v Hindustan Unilever Limited (TRA/1/2007/PT/MUM) IPAB held that:**
Moreover, it has to be stressed that the claims represent a generalisation of the examples and that is not a prerequisite for fulfilling the requirements of sufficiency of disclosure to provide an illustrative example for every possible specific combination encompassed by the claims. The claims represent generalisation of the examples and have to be read in a broad, technically meaningful way, but the functional terms should not be read in open contradiction with the whole content of the description. (To Include 9.2.3.2 of EP opposition)

The OPPONENT 2 ARGUED THAT same irrelevant since by the statements of the Applicant in the specification, in its reply statement dated March 3, 2017 and **by EVIDENCE** of the Applicant itself including the inventor, and the Opponent's expert affidavit that the broad scope of the 5 alleged invention is not supported and in fact not desired.

Knoll Pharmaceutical vs. Teva Pharmaceutical, are 367 F.3d 1381

To further demonstrate the unexpected activity of the claimed combination, Knoll submitted additional data directed to similar showings of efficacy. Three of the later studies submitted to the district court concerned the synergistic interaction of hydrocodone and ibuprofen when administered together for pain relief. The fourth study reported enhanced muscle repair after exercise following administration of the combination of hydrocodone and ibuprofen, an aspect not unrelated to pain relief. Evidence developed after the patent grant is not excluded from consideration, for understanding of the full range of an invention is not always achieved at the time of the filing the patent application. It is not improper to obtain additional support consistent with the patented invention, to respond to litigation attacks on validity. There is no requirement that an invention's properties and advantages were fully known before the patent application was filed, or that the patent application contains all of the work done in studying the invention, in order for that work to be introduced into evidence in response to litigation attack. Nor is it improper to conduct additional experiments and provide later-obtained data in support of patent validity.

The same is irrelevant since till date the case of the Applicant is on physico-chemical properties of a specific form of one compound and it has not been able to show any therapeutic effect.

The below case laws were relied upon by the Applicant **(portions as reproduced in the slides of the Applicant handed out at the hearing are reproduced below)-**

Teaching away – Sankalp Rehabilitation Trust vs. F Hoffmann-La Roche, OA/8/2009/PT/CH, IPAB i order 250/2012 characterize the person skilled in the art, para 42:
"He is neither picking out the" teaching towards passages" like the challenger, nor is he seeking out the "teaching away passages" like the defender"

Not routine experimentation – In re Stephen, US Federal Circuit Court,
"To have a reasonable expectation of success, one must be motivated to do more than merely to vary a parameters or try each of numerous possible choices until one possibly arrived at a successful result"

The aforesaid case-laws in fact highlight that absolute predictability is not required for testing obviousness and only a reasonable expectation is required for determining obviousness. The Applicant misled about the prior art including the prior art on co-crystal and thus the below case-laws of the Applicant on teaching away and not routine experimentation are irrelevant.

Thus the aforesaid, case-laws of the Applicant are irrelevant and passages taken selectively out of contextIn view the aforesaid grounds and submissions, the Opponent humbly prays that the impugned application be refused..

The opponent 3 & 6 submitted *the claims on record are very broad and claim compounds of valsartan and sacubitril wherein the ratio of the water in the complex is 0 to 3. There is no example or any guidance in the specification as to how a supramolecular complex can be formed when x is = 0 i.e. where water is not present. Similarly, there is no example to demonstrate as to how complex a complex can be formed when x is any value between 0 to 3 except 2.5. All examples pertain to a compound where x is = 2.5. This is important and relevant since the Applicant's own employee, PeterKarpinski has stated on oath that he had to conduct more than thousand experiments to arrive at the supramolecular complex where x is = 2.5. If the Applicant themselves have to conduct thousand experiments to arrive at a compound where x is = 2.5, it is but natural that arriving at a compound where x is any value from 0 to 3 except 2.5 would also involve equal number of experiments or undue experimentation.*

In view of the above, the claims are not properly supported by the specification and are liable to be rejected.

The opponent 4 submitted that the Applicant has failed to describe and disclose sufficiently in the complete specification:

- The best methods of developing the preferred embodiments of the compounds as claimed in claims 1 -5;
- The compounds comprising valsartan and sacubitril having 1 –3 moles of sodium and 0 -3 moles of water;
- The synthesis of the complex as claimed in Claim 6 -8 is too vague and will not teach a person skilled in the art to arrive at the claimed supramolecular structure;
- No clarity as regard to how the water molecules are associated to the compounds valsartan and sacubitril;
- The choice of alkali being Na+ finds no disclosure in the complete specification;
- The best dosage compositions of the preferred compounds inasmuch as the Patentee have provided only a generic composition of the effective drug containing any compound in claims 1-5.
- The Patentee has further failed to provide any ratios of the compound and excipients, failed to provide the effective dosage form and composition;
- The Patentee has also failed to provide the best methods of use of the said compounds. Further, the administration forms mentioned in the description are vague and too wide to include all possible routes of administration.

IV. **Post Filing of the data showing efficacy of the application not admissible**

Reliance is placed upon *Ajantha Pharma Vs Allergan Inc (MANU/IC/0060/2013),* attached herewith as **Annexure B** - The case has been cited for the proposition that post filing data cannot be accepted for obviousness analysis. This is categorically held in paragraph 93 of the order as reproduced herein below –

"… The respondent relied on the later study by Chen (inventor) in 2008 for a particular amount of the two components to prove the claimed striking advantages such as reduced side effects. We have said in earlier order No. 161/2003 that post filling evidence cannot be considered for obviousness analysis. We are not considering this evidence. Even otherwise, the evidence of nonobviousness in any case must match with the scope of the claims. We find the claims 1 and 20 as granted are not limited to the specific concentration of timolol component and bimatoprost component. Both the claims requires the presence of timolol component and bimatoprost component in an amount effective to reduce ocular hypertension (to the extent not specified) when applied to a hypertensive eye. Even this evidence will not change the position. We find this report and all other documents referred to in para ante are later to the priority date of the invention. We find them as not relevant in determining inventive step. Here we reiterate what we said in IPAB order No. 161/2013 "According to our Act, the patent is revoked if the invention is obvious. So the secondary considerations cannot change that." Therefore the secondary objective evidence is not relevant in determining non obviousness as per law. When we have found the claimed invention as obvious, we
are not inclined to accept the amendments in claims at last stage of hearing…."

Reliance is placed upon *Laboratorious Albiral Vs Bohringer (High Court of justice Chancery Division),* attached herewith as **Annexure C** - The case clarifies that the technical justification should be present in the patent 'as filed'. Documents cannot be filed to make good an internal deficiency in disclosure. The relevant paragraphs, 174 – 179, are given herein below –

"…

VII Speculative patents and ex post facto justification.

This topic also relates to the difficulties with para [0008]. Mr Waugh drew my attention to authority on sufficiency of disclosure in relation to 'speculative' or unsupported patents and the effect of after- acquired knowledge aimed at perfecting what would otherwise be a deficiency: see EPC, Art 83. This particularly applies to the relevance (if any) of the experiment which Boehringer chose to perform in this action so as to try to justify the statement in § [0008]

The upshot of such authority is this: sufficient justification for the solution to a technical problem must be found in the patent as filed. Experiments performed thereafter cannot be relied on at law to make good an initial deficiency of disclosure. It is not even enough that the teaching of

the patent is such that it is 'at least plausible' that what was proposed was capable of solving the problem it purports to solve. That said Mr Waugh, is applicable to this case. I agree.

The authorities relied on came from both domestic and EPO sources. From the EPO, Mr Waugh relied on Salk [T609/02] and Johns Hopkins [T1329/04]. Both were cases in the pharmaceutical field in which an element of speculation arose as to whether the claimed substances (a steroid hormone and a polypeptide, respectively) possessed the claimed therapeutic activity.

In Johns Hopkins, §12 the Board said: "The definition of an invention as being a contribution to the art i.e. as solving a technical problem and not merely putting forward one, requires that it is at least plausible by the disclosure in the application that its teaching solves indeed the problem it purports to solve. Therefore, even if supplementary post-published evidence may in the proper circumstances be taken into consideration, it may not serve as the sole basis to establish that the application solves indeed the problem it purports to solve."

. The EPO's approach to after-acquired knowledge is consistent with that taken in the United Kingdom. See for example the statement of Jacob J. (as he then was) in Richardson-Vicks' Patent [1995] RPC 568 at 581:

"Whether or not there was synergy demonstrated by experiments conducted after the date of the patent cannot help show obviousness or non-obviousness. Nor can the amended claim be better if only the components of the amended claim (as opposed to the unamended claim) can be shown to demonstrate synergy. The patent does not draw any such distinction and it would be quite wrong for later- acquired knowledge to be used to justify the amended claim.

***In Glaxo Group Ltd's Patents (supra) Pumfrey J. made** the following observations:*

Synergy

It is sometimes thought that a patent may be saved from a finding of obviousness if a combination otherwise obvious has some unexpected advantage, and, in particular, an advantage caused by an unpredictable cooperation between the elements of the combination. I do not consider that such an approach is in general justified. There is a limited class of cases in which the patentee has identified an advantageous feature possessed by some members only of a class otherwise old or obvious, has described the advantageous effect in his

specification and has limited his claim to the members of the class possessing this advantageous feature. Such a claim may be justified on the basis of what is called selection. Unexpected bonus effects not described in the specification cannot form the basis for a valid claim of this kind. I think that the matter is described with complete correctness by Jacob J in Richardson-Vicks' Patent [1995] RPC 568 at 581: [citing the passage referred to above] 114. If a synergistic effect is to be relied on, it must be possessed by everything covered by the claim, and it must be described in the specification. No effect is described in the present specification that is not the natural prediction from the properties of the two components of the combination. …"

V. Frivolous and Presumptive stand taken by the Applicant before the Hon'ble IPAB

> It is pertinent to note that the order dated 23.10.2020 passed by the Ld. Controller, against which the Applicant had preferred Appeal before IPAB had only deferred pre-grant proceedings till physical hearings are possible and had issued notice under Rule 55(3) of the Patents Rules, 2003 on the sixth and independent pre-grant opposition by one Mr. G Srinivas Rao.

The opponent 4 submitted that order dated 23.10.2020 was merely an order exercising the discretionary powers of the Ld. Controller as conferred upon him by Section of the Patents Act, 1970. .It is submitted that Applicant overreached its rights as practicing IP professionals to state any individual who files a pre-grant opposition is 'benami', and therefore is not eligible to challenge a patent. This is, of course, in direct contravention to the rights granted by the Indian Patent Law, which has been amended and enforced time and again to protect the rights of both the patentee as also the public of India. Specifically, under Section 25(1) of the Patents Act, 1970 'any person' may give a representation of opposition to a patent application in contrast to the opposition under Section 25(2) of the Patents Act, 1970 which is to be represented by only 'any person interested'..**Even so, the Applicant had not been able to establish any links whatsoever between Respondent nos. 3,5 and 6 with Respondent no. 4, i.e. Dr. Reddy's Laboratories, Ltd.**

The opponent 7 submitted that technically, supramolecular complex is a system or assembly of molecules which are associated with each other through intermolecular forces. “The complexes to be described herein all possess the following attributes: (1) They are composed of a minimum of two subunits. In short, phenomena analogous to protein folding, wherein a single molecule assumes a specific twoor three-dimensional structure, will not be covered. (2) The molecular architecture of these complexes is maintained by noncovalent interactions.”(Page 2230, para 2, Lawrence et al., “Self-Assembling Supramolecular Complexes”; Chem. Rev. 1995, 95, 2229-2260) Supramolecular complex is also called co-crystal. This is a routine practice in chemistry to make such compounds in order to resolve various issues.

The applicant submitted that there is sufficient enabling disclosure to prepare the compound, subject matter of the present application to a person skilled in the art. It is denied that the instant patent application is insufficient in respect of any description or that the claims lack clarity or are not supported by examples. *The applicant refers to and relies upon the contents of the present patent application in this regard. It is submitted that example do not limit the scope of the claimed invention in any manner and are merely added to enable the skilled person to perform the claimed invention without any undue experimentation. Therefore, the examples provided in the specification are sufficient enough to enable the skilled person to perform the claimed invention in its entire scope and that claims are sufficiently clear, without any ambiguity. The claimed compound is also clearly described, as Examples 1-3 which describe in detail the preparation of a compound comprising valsartan anions, sacubitril anions, sodium cations and water molecules in a molar ratio of 1:1:3:2.5.*

The applicant further submitted that the claims should be read in conjunction with the description. Hence, there is sufficient disclosure in the description that enables a skilled artisan to work the claimed invention. *The applicant further submitted that the invention claimed in the subject application and the method of working the invention i.e. the method of preparation of the supramolecular complex claimed in the present invention are described in detail in the specification and further exemplified, thereby providing clear guidance to a person of average skill to make the claimed compound in accordance with the present invention. The claims are clear and succinct and the scope of the claim clearly defines the metes and bounds of the invention.*

The applicant submitted that *The Opponent at the hearing with regard to ground of insufficiency made the following contention.*
a) Dr. Peter Karpinski affidavit (filed in US proceeding) – only hemipentahydrate is stable and tested, others undesirable.
b) Feng et al., is silent on stability of hemihydrate
c) Only one example has been disclosed in the specification, wherein hydration level is 2.5, i.e., hemipentahydrate. Therefore X should be limited to 2.5

The applicant further submitted that the Opponent once again has not even understood what the invention is about. The Applicant at the hearing, took the Ld. Controller through the patent specification of IN’4412 application to demonstrate that all the disclosures that is required under Section 10(4) of the Indian Patents Act is clearly contained therein.

The applicant argued that Applicant has not only disclosed the invention but has also disclosed the most preferred embodiment of the said invention in the patent specification

including its method for preparation. It is therefore submitted for "over disclosure" of the invention and disclosing the best embodiment and best mode of operation, the Applicant cannot be penalized. The case of the Opponent in relation to insufficiency is flawed not only scientifically but also legally. The Opponent makes a desperate attempt to suggest to the Ld. Controller that a person skilled in the art to whom the patent specification is addressed has absolutely no experience and no qualification in order to perform the invention as disclosed in the patent specification based on their experience and qualifications. Therefore, the patent specification according to the Opponent ought to be in the nature of manual wherein all the details which otherwise are in the knowledge of a person skilled in the art and common general knowledge should be a part of the specification under Section 10(4). THIS ARGUMENT IS SCIENTIFICALLY AND LEGALLY FLAWED IN VIEW OF THE INDIAN CASE LAW.

In law, as per Section 7 and S.10(4) & (5) of the Patents Act, 1970, there is a need for the Applicant

• to be in possession of the invention and
• to describe the invention in detail and provide the best mode of performing the invention.

The reason is that a person skilled in the art after expiry of the term of the patent should be able to reproduce the invention and perform it without the aid of the inventor or any other document.

This is also called the patent bargain where a person is required to disclose the invention in detail at the time of filing the application. The above is well illustrated by the judgement Teva vs. Pfizer (paras **31, 32, 33, 34**).

Tests to determine whether the claims are sufficient – Fully supported by the description:

The following are the rules or tests applied to check whether the claims are properly supported and fully described by the specification.

The entire scope of the claim must be properly enabled at the time of filing of the specification i.e each and every aspect and limitation of the claim must be either described or there must be some example. (Trustees of Boston University Vs. Ever Light Electronic Limited, 896F3D1357);

Whether undue experimentation is required to arrive at the embodiment. (Amgen Vs. Sanofi);

claim cannot include embodiments that are either inoperable or impossible to achieve or which does not lead to the invention – this would amount to misguiding the public at large (Trustees of Boston University Vs. Ever Light Electronic Limited, 896F3D1357)

- The argument that specification need not disclose the details fails when the thing alleged does not fall in prior art or is not available with the common general knowledge of a person skilled in the art;
- All the above tests must be applied as of the date of filing of the application and not thereafter.

Applying the above tests, one has to ascertain whether the entire scope of the claim i.e. the independent claim is fully enabled by the specification.

In the facts of the present case, none of the above rules are complied and hence the claims are insufficient and invalid.

Claimsaredrawntoembodimentsthatareeithernot possible to achieve or are inoperable - Hence the claimsareinsufficientand invalid:

Some of the claims of the present application are drawn to embodiments that are impossible to achieve or failures or matter that does not lead to the invention:

The claims include supramolecular complex of Sacubitril and Valsartan without the use of any solvent at all i.e. where x = 0 or in other words x is anhydrous. The claims also cover alternatives where x = 0.25 or 0.75 and other alternatives between 0 (anhydrous) and 1 However, there is no guidance in the specification or an example whereby any information can be gathered as to how to prepare a supramolecular crystal without the use of water- it is not even clear whether such a complex can be prepared at all- given that as per the Applicant themselves (Affidavit of Dr Motto para 5, 8, 10, 15 and Dr Karpinsky para 4), thousands of experiments and large number of resources/personnel/time were required to be carried out to arrive at a complex with 2.5 molecules of water.

If such huge amount of effort was required to generate complex with 2.5 molecules of water, equal amount if not less, would be required in order to arrive at complex with 0 (anhydrous form), 0.25 or 0.75 molecules of water.

Dr Karpinsky testifies that "undue experimentation" was required to arrive at a complex with 2.5 molecules of water. This fortifies the argument of the Opponent

that arriving at a complex whether having 0 (i.e. anhydrous form), 0.25, 0.75, 1, 2 or 3 molecules of water requires undue experimentation and is a "mini-research program" i.e a new invention;

When the Applicant themselves admit that a complex having 0 (i.e. anhydrous form), 0.25, 0.75, 1, 2 or 3 molecules of water requires huge amount of experimentation, then as per the settled law, the claims should be deemed to be not enabled by the specification and hence rejected on this ground alone.

Amorphous supramolecular complex is included in claim-1o As per Dr Motto – para 11- this amorphous form is less desirable Thus, claim 1 includes embodiments that are either not desirable or less preferred.

Claim 6 : Step (i) of claim 6 reads as under: "dissolving (S)-N-valeryl-N-{[2'-(1H-tetrazole-5-yl)-biphenyl-4- yl]-methyl}-valine or a salt thereof and (2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2- methylpentanoic acid ethyl ester or a salt thereof in asuitablesolvent"

The said claim includes within its fold any and every solvent in the chemistry text book – some of which may work and some may not even work.

The specification (Page 35) lists out some solvents- such as "Solvents included in the scope of the present invention include, but are not limited to, solvents in which the ARB, NEPi and inorganic salt forming agent preferably exhibit a lower solubility that allows the linked pro-drug to crystallize. Such solvents may comprise, but are not limited to, water, methanol, ethanol, 2-propanol, ethylacetate, methyl-1- butylether acetonitrile, toluene, and methylene chloride and mixtures of such solvents"

The said claim 6 is thus not fully supported by the specification as all the solvents in the text book of chemistry are neither illustrated nor enabled by the specification. The entire range of the claim is not enabled.

As per claim 6 (ii), "the sodium compound is dissolved in a suitable solvent"

The term 'sodium compound' is broad enough to include any compound having sodium eg. sodium bicarbonate. These compounds are stated on page 35 of the specification

"The inorganic salt forming agent includes, but is not limited to, calcium hydroxide, zinc hydroxide, calcium methoxide, calcium acetate, calcium hydrogen carbonate, calcium formate, magnesium hydroxide, magnesium acetate, magnesium

formate and magnesium hydrogen carbonate, sodium hydroxide, sodium methoxide, sodium acetate, sodiumformate.

The inorganic salt forming agent releases the linking moiety into the solvent such that when an ARB and a NEPi are present a linked pro-drug is formed".

However, as per the Affidavit of Dr Motto (para 4 read with para 8) - none of these salt forming agents zinc hydroxide, calciummethoxide, magnesiumhydroxide, sodium methoxide, sodium hydroxide, potassium hydroxide, lithium hydroxide monohydrate, ammonium hydroxide lead to crystalline material/solid.

The relevant portion of the affidavit of Dr Motto is reproduced hereunder: "4. These various combinations, along with numerous solvent choices were explored experimentally utilizing high- throughput screening (HTS) techniques. The inorganic SFA's tried in these exploratory HTS experiments were zinc hydroxide, calcium methoxide, magnesium hydroxide, sodium methoxide, sodium hydroxide, potassium hydroxide, lithium hydroxide monohydrate, ammonium hydroxide. The solvents used in these experiments are listed in the table below":

Neat Solvents	Binary solvent mixtures
Water	ethanol-water
Methanol	methanol-water
Ethanol	2-propanol-water
2-propanol	acetonitrile-water
ethyl acetate	acetone-water
methyl-t-butyl ether	2-propanol-toluene
Acetonitrile	ethyl acetate-heptane
Toluene	methyl-t-butyl ether-
methylene chloride	toluene-heptane

The opponent no 7 argued that none of the experiments led to crystalline material or generated solids. The fact that the simplest possible system, ethylene diamine, failed to produce crystalline solids, suggests that formation of VAL-AHU double salts with divalent organic bases would be very unlikely." Therefore, this claim is broad enough to include impossible to perform alternatives - the claim is rather misguiding the public. Since the claim includes embodiments that are unworkable, the claim should be rejected.

The opponent 7 further argued that Claims are drawn to embodiments which require undue experimentation-Hence the claims are insufficient and invalid:

No enablement or support for crystalline complex where hydration state is x=0-3 where x=0 refers to anhydrous form:

Claim 1- is drawn to a supramolecular complex, which comprises:

- Valsartan anions; and
- NEP inhibitor (2R,4S)-5-biphenyl4-yl-5-(3-carboxy- propionylamino)-2-methyl-pentanoic acid ethyl ester) anions
- Sodium cations.
- Water molecules - x wherein x is 0 (anhydrous form) to 3(hydration state)

The Opponent 7 argued that there is no guidance or a working example as to how one can obtain a crystalline supramolecular complex of Sacubitril and Valsartan without the use of any solvent at all i.e. where x = 0 (anhydrous form) or to obtain supramolecular complex with 0.25 or 0.75 water molecules.

Further, there are working examples 1-3, which describe in detail and illustrate how to obtain a supramolecular complex; it is pertinent to note that examples 1-3 are illustrative of a case where

- 0.41g of Valsartan are combined with 0.42g of Sacubitril, 0.111g of sodium ions and 7ml of water

- 10g of Valsartan are combined with ~ 10g of Sacubitril, 2.76 g of sodium ions and 8 ml of water

- 1.984 kg of Valsartan are combined with 2.00 kg of Sacubitril, 547.6 g of sodium ions and 1.0L of water

In other words, the product that is obtained as a result of examples 1-3 is a supramolecular complex in the form of hemipentahydrate i.e water hydration state of the complex is 2.5

It is further pertinent to note that Dr. Motto, in his affidavit (para 15) filed before this Patent Office confirms and asserts that after 8 months of experiments and great effort, they could arrive at supramolecular complex with 3 sodium ions and 2.5 molecules of water;

Similarly, Prof Dr Karpinsky (annexure J of the opposition) also confirms that they had to do thousands of experiments in order to arrive at a crystalline complex with valsartan-sacubutril anions, 3 sodium cations and 2.5 water molecules (in 1:1:3 ratio)

The specification or the examples do not specify anything about a supramolecular complex with 0 (anhydrous form), 0.25, 0.75, 1, 2 or 1.5 or 3 molecules of water or even.

Even Dr Motto or Dr Karpinsky make no effort to explain how a supramolecular complex with 0 (anhydrous form),0.25, 0.75, 1, 2, 3 or 1.5 molecules of water can be obtained – please see examples 1-3 - whether 8ml water or 7ml water or 1 litres of water will yield supramolecular complex with 1 molecule of water is not known from the specification.

It is logical to conclude that since the Applicant alleges to have conducted thousands or hundreds of experiments to arrive at a supramolecular complex, as claimed, similar number of experiments would be required to obtain supramolecular complex where x = 0 (anhydrous form), 0.25, 0.75, 1, 2 and 3. No roadmap or guidance is provided by the specification as to what conditions will lead to a supramolecular complex wherein x = 0 (anhydrous form), 0.25, 0.75, 1, 2 and 3. Thus, a person skilled in the art would have to undertake several hundred experimentations in order to arrive at a supramolecular complex where x = 0 (anhydrous form),, 0.25, 0.75, 1, 2, 3 etc. This represents undue experimentation, which is precisely what the provision of Section 10(5) & (6) to avoid. The Applicant cannot be given liberty to keep any part of the invention as a trade secret and allege that it would be known to a person skilled in the art.

Thus, undue experimentation would be required in order to arrive at a supramolecular complex with x=0-3 molecules of water, where 0 refers to anhydrous form. When this was pointed out by Dr Karpinsky in US – the US Patent office directed the Applicant to restrict their claims and the claims were restricted. Thus, there is no enablement for the claims across the breadth i.e for x=0-3 (where 0 = anhydrous form)

Rebuttal to the Response of Applicant:

The response of the Applicant to the above arguments was primarily that:

- the specification properly enables the claims;
- a person skilled in the art is a man capable of reading and understanding the claims and the specification and would be able to perform the invention without undue experimentation (re - Sankalp vs. F. Hofmann-La Roche AG)

The above arguments are entirely contrary to record because:

- the Applicant's own expert Dr Karpinsky and Dr Motto have testified specifically that it would require thousands of experiments and undue experimentation to arrive at the supramolecular complex having a hydration state with 2.5 molecules of water – if this is true, then this is beyond the capacity of a person skilled in the art;
- a person skilled in the art for purposes of section 25(1)(g) is a person of average knowledge in the art- he has no ingenuity- he has no creativity. He can only follow the instructions as stated in the specification – the specification is as mute as the Sphinx and therefore not enabling.

There is not any guidance or direction to prepare – as there is no process – it is not certain from the specification whether the same process or some other process or any variation in the process is required to achieve these hydration states- it is also not clear whether a commercially viable product will be obtained and if obtained whether it will be amorphous or crystalline.

No patent can be granted for an invention that the Applicant was never in possession of at the time of filing:

It is settled law (sec 7(4)) that an Applicant should be in possession of the invention as of the date of its filing;

As stated in the foregoing paragraphs, the specification does not fully support the claims, nor is the range of ingredients claimed supported by the specification;

This is because the Applicant was never in possession of the invention as of the date of filing;

There is nothing in the specification which would guide a person skilled in the art to arrive at:

- an amorphous complex where the hydration state is x=0- 3, (where x=0 refers to anhydrous form);
- a crystalline complex where the hydration state is x=0-3 (where x=0 refers to anhydrous form)

There is no such disclosure since the Applicant never knew of such a complex at the time of filing. Therefore the Applicant was not in possession of the invention as claimed.

When a claim is made to a compound that is not possible to achieve or is impossible to make or is less desirable, or if made has no utility- then the third limb of invention i.e industrial application (novelty, inventive step and industrial application) would fail and the invention cannot be patented (In Teva Vs. Pfizer, para (e), pg. 642)

No claim can be granted for something the Applicant never invented – hence due to lack of enablement, claim 1 is insufficient and invalid. Clearly the claims include embodiments that do not work [where x = 0 (anhydrous form), 0.25 or 0.75]. Further, the impugned application ought to be rejected as the said claim No. 1 and other claims are not enabled across the entire scope of the claim and it includes embodiments that do not even work.

Granting such a claim would amount to practising fraud on the public as the public would only have the patent to refer to after the expiry of its term. The public will practice the claim and find that the claims are not workable.

Dr. Motto's affidavit:

a) Salt-forming agents

The opponent no 7 submitted that Dr. Motto, as per his affidavit, joined Novartis (the Applicant) only in 2007 – the present application has a priority year of 2005. So by the time Dr Motto had joined, the alleged invention would have presumably already been conceived, hence Dr Motto has no personal knowledge of the facts stated;

As per para 4 several salt forming agents were attempted- these include "....zinc hydroxide, calcium methoxide, magnesium hydroxide, sodium methoxide, sodium hydroxide, potassium hydroxide, lithium hydroxide….". However, as per para 8, Dr Motto clearly and categorically states that "none of the experiments lead to crystalline material or generated solids". It is notable that the specification at page 35 describes and lists out various salt forming agents and included within this is, sodium hydroxide and sodium methoxide, which as per Dr. Motto do not work;

As per para 12, the experiment with sodium hydroxide yielded amorphous film – and only calcium yielded crystalline solid. However suddenly in para 14, it is stated that crystalline solid was obtained with sodium, potassium or calcium which cannot be true. Not only was double salt obtained, it is stated in para 16 that crystalline solid was seen with Na cation.

Thus everything which is stated to be correct as per the specification – Dr Motto says that they cannot be done, or are unsuccessful which itself is a ground rejection of the application.

The applicant further argued that for insufficiency, the test to be applied is as follows:

a) What is the invention; and

b) Can a person skilled in the art who based on reading of the specification, their qualifications, experience, and common general knowledge be able to perform the invention without undue experimentation under Section 10(4) of the Indian Patents Act.

The applicant submitted that The patent specification of IN'4412 application clearly meets all the four corners of the said provision. Section 10(4) states as follows:

"*Every complete specification shall-*

(a) fully and particularly describe the invention and its operation or use and the method by which it is to be performed;

(b) disclose the best method of performing the invention which is known to the applicant and for which he is entitled to claim protection; and

(c) end with a claim or claims defining the scope of the invention for which protection is claimed;

(d) be accompanied by an abstract to provide technical information on the invention.

Section 10(4)(b) only requires the best method for performing the invention known to the Applicant to be disclosed and that the claims should define the scope of the invention.

Therefore, there are two critical features of Section 10(4) namely:

a) What is an invention and

b) Scope of the claims which should be commensurate to the disclosure made by the Applicant in the patent specification keeping in mind that the patent specification is addressed to a person skilled in the art.

Further, the objection of the Opponent that the claims should only be limited to the hemipentahydrate because there is allegedly only one example is completely flawed and contrary to the lawinIndia.

The Applicant relies on the following decisions:

1) *A patent specification is addressed to a person skilled in the art*
2) *Extent of disclosure in the patent specification*

a) F.H. and B. Corporation v. Unichem Laboratories, [AIR 1969, Bom 255]

enclosed as ***Annexure-5***

14. Dealing first with the ground of insufficiency of description it is stated in Halsbury, (3rd edn.) Vol. 29 p. 64 para 131 that the claim need only be as clear as the subject admits, and that a patentee need not so simplify his claim as to make it easy for infringers to evade it…..[I]t is further stated in the same Volume of Halsbury (p. 66 para 138) that insufficiency of description has two branches, (1) the complete specification must describe ***"an embodiment"*** *of the invention claimed in each of the claims and that the description must be sufficient to enable those in the industry concerned to carry it into effect "without their making further inventions"; and (2) that the description must be fair i.e. it must not be unnecessarily difficult to follow.[*

*. …[****Tlhe specification and claims are addressed to those with a high degree of knowledge of the field of science to which they relate, particularly when they relate to chemistry and allied subjects. It is not necessary to describe processes on the Claims to a specification when they are part of the common knowledge available to those skilled in the science who can, after reading them, refer to the technical literature on the subject for the purpose of carrying them into effect.*** *"An embodiment" of the invention is, therefore, in my opinion, sufficiently described in the plaintiff's patent and that description is not unnecessarily difficult to follow, it being sufficient to enable the invention to be carried into effect "without making further inventions".*

As stated by Halsbury (3rd Edn.) Vol. 29 p. 59 Para. 123, ***"not useful" in patent law means that the invention will not work, either in the sense that it will not operate at all or more broadly, that it will not do what the specification promises that it will do. If the invention will give the result promised at all, the objection on the ground of want of utility must fail. It is further stated in the said passage that the practical usefulness or commercial utility of the invention does not matter, nor does it matter whether the invention is of any real benefit to the public, or particularly suitable for the purposes suggested, and that it is only failure to produce the results promised that will invalidate the patent, not misstatements as to the purposes to which such results might be applied.***

3) *Characteristics of a person skilled in the art.*

a) Roche vs. CIPLA, RFA 92/2012 enclosed as ***Annexure-6***

The ***Division Bench of Hon'ble Delhi High Court, in Roche vs CIPLA, 2015*** *in para 112 held that*

"to test obviousness" the first test required to be applied is ***to see who is an ordinary person skilled in art*** *(POSA) and its characteristics. The features of a person skilled in the art are*

i. *that of a person who practices in the field of endeavour,*
ii. *belongs to the same industry as the invention,*
iii. *possesses average knowledge and ability and*
iv. *is aware of what was common general knowledge at the relevant date.*

b) Sankalp Rehabilitation Trust Vs. F. Hoffmann-La Roche AG, IPAB (Order

No. 250/2012) enclosed as ***Annexure-7***

In OA/8/2009/PT/CH, the Hon'ble IPAB in [para 42] held as follows:

"[Para 42] ….this man is "A person of ordinary skill is also a person of ordinary creativity not an automaton."….
We must remember that this ordinary man has skill in this art. He is not ignorant of its basics, nor is he ignorant of the activities in the particular field. He is also not ignorant of the demand on this art. "He is just an average man..... Well... just an ordinary man." But he is no dullard. He has read the prior art and knows how to proceed in the normal course of research with what he knows of the state of the art.
A person of ordinary skill reads the ***prior arts as a whole*** *and allows himself to be taught by what is contained therein.* ***He is neither picking out the" teaching towards passages" like the challenger, nor is he seeking out the "teaching away passages" like the defender****. …*

4) *Claims need not be limited to working examples as scope of the claims under Section* 10(4) have to commensurate to the disclosure made in the patent specification.

a) In FDC Ltd vs Sanjeev Khandelwal and Ors, Hon'ble IPAB, (OA/15/2009/PT/MUM) enclosed as ***Annexure-8*** stated as follows

As per section 10(4) every complete specification shall fully and particularly describe the invention and disclose the best method of performing the invention which is known to the applicant. However, it is not mandatory that the claims should be representative of the best method. The Controller suggested amendment in claim 13 only for clarity purpose i.e. for bringing claim 13 in line with the claim 1. The clarity issue cannot be correlated to insufficiency of description.

b) Tata Global beverages Limited vs. Hindustan Unilever Limited, Hon'ble IPAB, 2012 SCC Online IPAB 162 *enclosed as* ***Annexure-9*** **stated as follows:**

Moreover, it has to be stressed that the claims represent a generalization of the examples and that it is not a prerequisite for fulfilling the requirements of sufficiency of disclosure to provide an illustrative example for every possible specific combination encompassed by the claims. The claims represent generalizations of the examples and have to be read in a broad, technically meaningful way, but the functional terms should not be read in open contradiction with the whole content of the description.
Hence, the board is convinced of the completeness of the description and that the skilled person in the field of pharmaceutical technology is able to carry out the claimed invention."

[

c) The **Hon'ble Supreme Court of India in Bishwanath Prasad Radhey Shyam Vs Hindustan Metal Industries (AIR1982SC1444)** enclosed as ***Annexure-10***

stated as follows as follows:

As pointed out in Arnold v. Bradbury (1871) 6 Ch. A. 706 the proper way to construe a specification is not to read the claims first and then see what the full description of the invention is, but first to read the description of the invention, in order that the mind may be prepared for what it is, that the invention is to be claimed, for the patentee cannot claim more than he desires to patent. In Parkinson v. Simon (1894) 11 R.P.C. 483 Lord Esher M.R enunciated ***that as far as possible the claims must be so construed as to give an effective meaning to each of them, but the specification and the claims must be looked at and construed together.***

The learned trial Judge precisely followed this method of construction*. He first construed and considered the description of the invention in the provisional and complete specification, and then dealt with each of the claims, individually.* ***Thereafter, he considered the claims and specification as a whole, in the light of the evidence on record.***

(B) DISCLOSURE OF THE INVENTION IN THE PATENT SPECIFICATION

The Applicant argued that he has in an unambiguous manner made a very clear disclosure in the patent specification. The content of aforesaid section in *paras 21 to 25* are not repeated for the sake of brevity.

a) Under the head of "field of invention", **the Applicant has stated** that the present invention is directed to ***dual-acting compounds*** and combinations of angiotensin receptor blockers and neutral endopeptidase inhibitors, in particular, a dual acting compound wherein the angiotensin receptor blocker and neutral endopeptidase inhibitor are linked via non-covalent bonding.

b) Under the head 'Detailed description', the Applicant clearly provides the invention as being a dual acting compound wherein two active compounds with different mechanism of action namely an angiotensin receptor antagonist and a neutral endopeptidase inhibitor can form a unique supramolecular entity for the treatment of patients with various cardiovascular and/or renal diseases.

c) Further, the patent specification clearly provides that the new supramolecular entity has distinct properties different to the physical combination as defined on page 9 of the patent specification of IN'4412 application.

d) The supramolecular compound has also been defined as an "interaction" between the two actives to form a single compound.

The Applicant argued that the applicant has extensively disclosed the process of preparing the novel compound according to the present invention. *Reference in this regard is made to pages 37-41 of the specification of IN'4412 application.*

a) The specification further provides that the preferred molar ratio of Valsartan: Sacubitril in the compound is 1:1.

b) Further, with regard to the sodium cation, the specification further provides on page 22 that the preferred molar ratio in which Valsartan, Sacubitril and sodium cation is present is 1:1:3.

c) Therefore, the stoichiometric ratio of **Valsartan to Sacubitril to Sodium** in the preferred compound and also commercial product of the Applicant derived pursuant to IN'4412 is in the ratio of 1:1:3 that is specifically claimed by claims 1 to 3.

d) The hydration state of the said novel compound is also within a **narrow range** of 0-3 such as 0, 0.25, 0.5, 0.75, 1.25, 1.5, 1.75, 2.25, 2.5, 2.75, 3, preferably 2.5.

The applicant further argued that the dual acting compound of the present invention is characterized by very distinct spectral peaks and shifts that are not observed in the physical mixture. The preferred embodiment, '*tri-sodium-[3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1- butylcarbamoyl)-propionate-(S)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}-amino)butyrate]-hemipentahydrate*' is exemplified in Examples 1-3 of the IN'4412 Application (*p. 40-43*) and is fully characterized by various analytical and spectroscopic techniques (*p. 24-29 and 43-45 of the specification*). The single crystal X-ray diffraction (SCXRD) data for the exemplified embodiment of the claimed supramolecular compound reveal a highly unusual and intricate three- dimensional structure, as summarized on *page 28* of the specification of the IN'4412 Application.

(C) POSA WOULD BE ABLE TO ACHIEVE DIFFERENT HYDRATION LEVEL

The applicant submitted that the argument of the Opponent that claims should be limited to hemipentahydrate since only one example for 2.5 hydrate (hemipentahydrate) has been disclosed in the specification is flawed scientifically and legally.

The Applicant further submitted that the preferred embodiment "hemipentahydrate wherein "x" is 2.5' *(see p. 22, second to last paragraph of the specification of the IN'4412 application)* has been exemplified in Examples 1-3. Further, the compound in which x = 0.5 (hemihydrate) is disclosed in Example 3 of the specification. In example *3 at page 43 and page 46 of the patent specification of IN'4412 application,* the Applicant clearly states as follows:
"*As shown by DSC and thermogravimetric analysis (TGA), upon heating, the water of hydration is released in two steps: the first step occurs below 100°C and the second step above 120°C. Both DSC and TGA instruments are operated at a heating rate of 10 K/min*."

Example 3 (*reference is made to Dr. Myerson affidavit para 2.10*) describes that a person skilled in the art would be able to vary the hydration level. The differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) showed that upon heating the

water of hydration is released gradually from the exemplified hemipentahydrate compound in two steps: the first step occurs below 100°C and the second step above 120°C. The loss of water in two steps in DSC/TGA studies – one step below 100°C and the second step above 120°C – is characteristic of a compound with multiple hydration states. During the first dehydration step, 80% of the water of hydration is lost (equivalent to two water molecules), yielding a hemihydrate compound (i.e. x = 0.5).

The applicant argued that the specification provides general methods which can be used to provide compounds of the invention. These methods are not limited to the formation of crystalline forms. *For example, page 37, line 18 to page 40, line 24 of the specification* describe in detail methods of preparing a dual-acting compound such as that of claim 1 by: (i) dissolving an angiotensin receptor antagonist (in this case Valsartan) and a neutral NEPi (in this case Sacubitril) in a suitable solvent, (ii) dissolving a basic compound of Cat (in this case sodium) in a suitable solvent, (iii) combining the solutions of steps (i) and (ii), (iv) precipitating the solid and drying the same to obtain the dual-acting compound (of claim1) or obtaining the dual-acting compound (of claim 1) by solvent exchange. At no point is the method described as being limited to the formation of a crystalline form of the claimed compound.

Additionally, the amorphous compound is obtained as an intermediate in Example 1 of the Patent. In Example 1, a 1:1:3 molar ratio of Valsartan, Sacubitril and sodium hydroxide are dissolved, combined and stirred. The solution is evaporated to yield a glassy solid. The glassy solid is an amorphous form of the claimed compound. While this glassy solid is an intermediate, not a final product, in Example 1, that does not cast doubt on a single compound being obtained. A scientist could stop the experiment reported in Example 1 after the glassy solid was obtained and thus obtain the glassy solid as the final product.

Reference is also made to the *Opinion of the Opposition Division opinion in patent EP'828 that in paragraph 9.2.3.2* states as follows:
"In particular, it is apparent from example 1 that a glassy solid was obtained as an intermediate product. The opposition division takes this as proof that a polymorphic form was prepared in a form that allows for isolation."

These facts are indicative of the following:
a) A person skilled in the art to whom the patent specification is addressed will clearly recognize the invention is in combining Valsartan and Sacubitril into a single compound, preferably with a 1:1 stoichiometric ratio of Valsartan ions: Sacubitril ions.

b) Claim 1 is represents a generalization of the invention and includes the exemplified most preferred embodiment of the invention.

c) With regard to stoichiometric ratio, a person skilled in the art can derive the stoichiometric ratio based on the disclosure in the patent specification on page 22.

d) The claimed compound can be a hydrate or anhydrous. Methods to change the hydration status of a compound are typically known to a person skilled in the art.

e) The claimed compound can be in amorphous or crystalline form. Methods to make solid forms of a compound are typically known to a person skilled in the art.

f) Example 3 at pages 43 and 46 clearly show how the hydrate state can be varied, which is well known to a person skilled in the art and further supported also by Feng et al.

g) The claims as per the Indian Patent law and case law need not be limited to the exemplified compounds as the said disclosure of the most preferred embodiment and best method was made by the Applicant under Section 10(4). The law as interpreted by the courts of India clearly state that

a. The invention has to be gleaned from the patent specification and the specification has to be read in **entirety to understand the invention;**

b. POSA is entitled to carry out routine experimentation once the said disclosure is made as POSA is not a dullard;

c. Claims need not be limited to the examples as claims represent a generalisation of the examples and that it is not a prerequisite for fulfilling the requirements of sufficiency of disclosure to provide an illustrative example for every possible specific combination encompassed by the claims.

Further, a person skilled in the art would be able to make the claimed compound in crystalline or amorphous form using the disclosure of the IN'4412 application. In the US, both amorphous (US11,096,918 enclosed as ***Annexure-11***) and crystalline (US8,877,938 enclosed as ***Annexure-12***) form have been granted based on the same disclosure as of IN'4412 application.

What is claimed is:

1. An amorphous solid form of a compound comprising anionic (S)-N-valeryl-N-{[2'-(1H-tetrazole-5-yl)-biphenyl-4-yl]-methyl}-valine, anionic (2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester, and sodium cations in a 1:1:3 molar ratio.

US8877938

What is claimed is:

1. Trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2"-(tetrazol-5-ylate)biphenyl-4'-ylmethyl}amino)butyrate] hemipentahydrate in crystalline form.

US11,096,918

Further, even EP2340828 has been granted with x=0-3 (i.e. same as in India) encompassing all solid forms (crystalline and amorphous).

(D) <u>Dr. Piotr H. Karpinski</u>

Further, Opponent's reliance on the affidavit of Dr. Piotr H. Karpinski, filed during the prosecution of the **US patent no. 8,877,938**, in that 1000 of experiments required to be performed in order to achieve 2.5 hydrate form is totally flawed.

The Applicant submitted that Dr. Karpinski's (inventor) affidavit was submitted before USPTO during the prosecution of US patent no. 8,877,938 in response to the objection of obviousness raised by the USPTO. It is pertinent to note that the USPTO raised the objection of inventive step and Dr. Karpinski's affidavit deals with the objection of obviousness and not insufficiency. In this regard, the Applicant draws attention towards the notice of allowance of US8,877,938 patent, enclosed as ***<u>Annexure-</u>***

4. The following is an examiner's statement of reasons for allowance: The Examiner has reconsidered the Declaration of Piotr H. Karpinski, filed 9/9/2010 together with the arguments filed 6/23/2011 and 12/17/2013. The arguments are persuasive. The Declaration establishes over 1000 experiments were required to prepare the claimed crystalline compound. This demonstrates undue technical hurdles and provides evidence of unpredictability. When weighed together with the prior obviousness basis, the difficulty to prepare the claimed compound is a secondary consideration sufficient to render the claims non-obvious. Since the amended claims, as allowed are commensurate in scope with the Declaration evidence, the obviousness rejection has

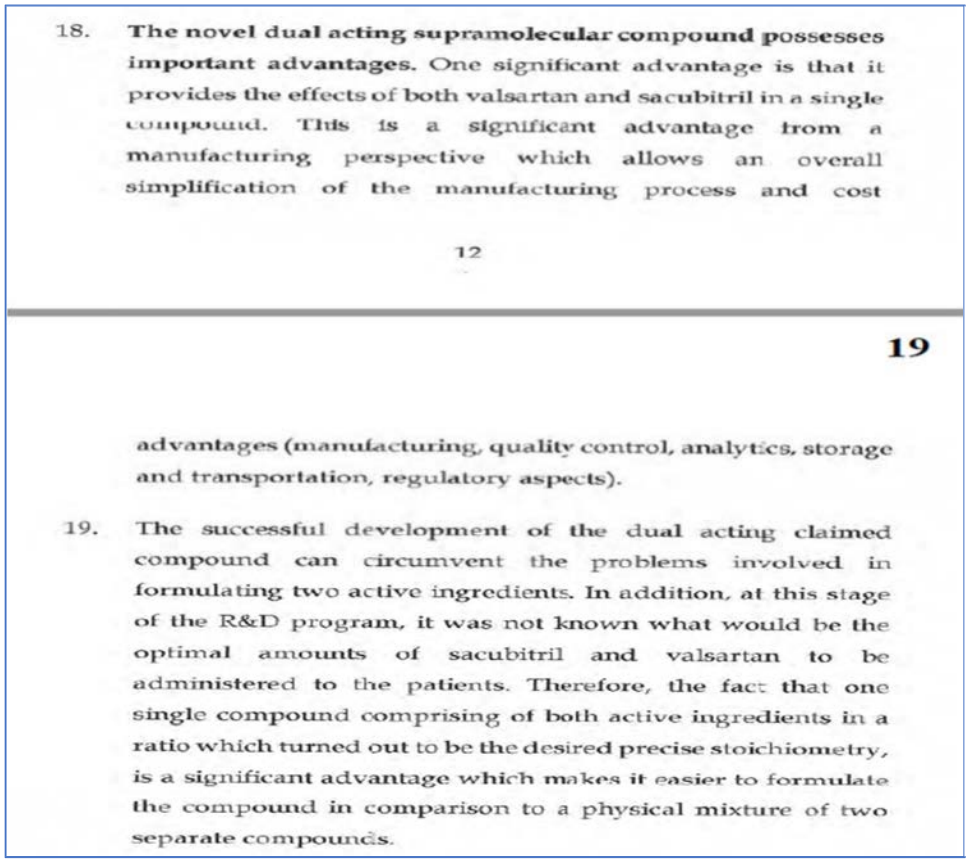
As evident from above, Dr Piotr H. Karpinski affidavit filed before USPTO was in relation to 'Obviousness' and not 'Insufficiency'. The USPTO in the 'notice of allowance' clearly highlighted that over 1000 experiments were required to prepare the claimed crystalline

compound, which demonstrates **undue technical hurdles and provides evidence of unpredictability** in achieving the claimed invention.

The applicant argued that the argument of the Opponent in relation to Dr. Karpinski affidavit is completely flawed.

(E) EXPERIMENTATION TO ARRIVE AT THE CLAIMED INVENTION vs. EXPERIMENTATION TO PERFORM THE DISCLOSED INVENTION.

The Applicant submitted that **Dr. Motto in his affidavit** in particular para 3 has clearly identified the invention upon which the inventors of IN'4412 embarked an ***experimental quest***. The research carried out by the inventors of IN'4412 as stated in para 3 was to unite Sacubitril and Valsartan into a single chemical entity. Further, *Dr. Michael Motto in para 3 of his affidavit* documented various strategies adopted by the inventors of IN'4412 application and their failure.



18. **The novel dual acting supramolecular compound possesses important advantages.** One significant advantage is that it provides the effects of both valsartan and sacubitril in a single compound. This is a significant advantage from a manufacturing perspective which allows an overall simplification of the manufacturing process and cost

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advantages (manufacturing, quality control, analytics, storage and transportation, regulatory aspects).

19. The successful development of the dual acting claimed compound can circumvent the problems involved in formulating two active ingredients. In addition, at this stage of the R&D program, it was not known what would be the optimal amounts of sacubitril and valsartan to be administered to the patients. Therefore, the fact that one single compound comprising of both active ingredients in a ratio which turned out to be the desired precise stoichiometry, is a significant advantage which makes it easier to formulate the compound in comparison to a physical mixture of two separate compounds.

In paras 18 and 19, Dr. Motto states that the ***novel dual acting supra molecular compound comprising the two active ingredients in a specific ratio has significant advantages.***

Dr. Michael Motto's affidavit highlights the difficulties and unpredictability to unite Sacubitril and Valsartan into a single chemical entity. Dr. Motto's affidavit clearly shows that it was **NOT a routine technique** to combine two active pharmaceutical ingredients ("APIs") into a single compound at the priority date. There was simply no precedent or expectation at the priority date for the formation of a single compound comprising Valsartan or Sacubitril, let alone a single compound comprising both APIs in the form of anions at the therapeutically desirable 1:1 molar ratio, together with sodium cations and optionally water molecules.

The focus of Dr. Michael Motto affidavit was to deal with the issue of inventive step and to demonstrate that the research that led to LCZ696 and ultimately to the final commercial product Vymada cannot be considered as a routine experimentation. Dr. Motto clearly makes a point that the said research was challenging.

The applicant argued that Thus, **Dr. Motto's affidavit** is in relation to "experimentation that led to the claimed invention to address non-obviousness"- research prior to the filing of the application whereas the **Opponent is misreading the affidavit as "experimentation to perform the claimed invention**" so as to deal with the ground of insufficiency.

(F) EP OPPOSITION- PRELIMINARY OPINION OF THE EP OPPOSITION BOARD

The Applicant further relied upon the preliminary decision of the EPO enclosed as ***Annexure-14*** in the 8 opposition proceedings filed against the EP2,340,828 B1 patent (EP'828 patent). Claim 1 of **EP '828** patent is reproduced below:

Claim 1 of EP2,340,828 B1

A compound having the sum formula [((S)-N-valeryl-N-{[2'-(1H-tetrazole-5- yl)-biphenyl-4-yl]-methyl}-valine) ((2R,4S)-5-biphenyl-4-yl-4-(3-carboxy- propionyl-amino)-2-methyl-pentanoic acid ethyl ester)] Na3 • x H2O, wherein x is 0 to 3, and being in the solid form.

9.2.3 The opposition division currently opines that the claimed subject-matter is sufficiently enabled:

9.2.3.1 Documents D9 and D64 disclose that at the priority date it was common practice in the field of pharmaceuticals to apply standard techniques in order to screen for hydrates or polymorphs.

It has not been substantiated that other hydrates or polymorphs than the

The said claim is similar to the claims currently pending in India in the IN '4412 application. The EP Opposition Board in their preliminary opinion clearly held the claimed invention as sufficiently enabled. The relevant extract from the EP opposition is as follows:

9.2.3 The opposition division currently opines that the claimed subject-matter is sufficiently enabled:

9.2.3.1 Documents D9 and D64 disclose that at the priority date it was common practice in the field of pharmaceuticals to apply standard techniques in order to screen for hydrates or polymorphs.

It has not been substantiated that other hydrates or polymorphs than the

9.2.3.2 However, even disregarding D16, D17, D67 and D68 the opposition division currently opines that it is plausible from the patent alone that further hydrates and polymorphs can be obtained.

In particular, it is apparent from example 1 that a glassy solid was obtained as an intermediate product. The opposition division takes this as proof that a polymorphic form was prepared in a form that allows for isolation.

Moreover, example 3 of the patent discloses that the hemipentahydrate, upon heating, looses 80% of its water, thereby forming a compound according to claim 1 with x being 0.5.

The Applicant submitted that in relation to sufficiency, the scope of claim 1 is commensurate to the technical contribution provided in the specification of the IN'4412 application. The IN'4412 application relates to a new compound, which is claimed as different hydrates. Although, the IN'4412 application does not exemplify each and every hydrate within the scope of the claims, there is no requirement for the claims to be limited to the particular physicochemical form(s) that have been specifically exemplified in the description (*case law, FDC Ltd vs Sanjeev Khandelwal; and Tata Global vs HUL*). On the contrary, it is well established that disclosure of one way of making a new compound is sufficient to justify a claim that covers the compound and its derived forms in any physical form in which they may be obtained. This is because once a skilled person is given a new compound, variants such as polymorphs and hydrates would be considered routine to make using common general knowledge. Therefore, the opponents' objections regarding the scope of the claims should be rejected.

In view of our above submissions, the said ground of opposition should be dismissed in-*limine*.

(4) US FDA GUIDANCE DOCUMENT IS IRRELEVANT

Dr Dandala has relied on the definition of pharmaceutical co-crystal from the US FDA guidance document.

The Applicant submitted that the Opponent once again has not even understood what the invention is about. The Applicant at the hearing, took the Ld. Controller through the patent specification of IN'4412 application to demonstrate that all the disclosures that is required under Section 10(4) of the Indian Patents Act is clearly contained therein.
At the outset, the US FDA guidance document is not a relevant prior art document since it was published, February 2018, after the priority date of IN '4412 application,

I. INTRODUCTION

This guidance provides applicants planning to submit new drug applications (NDAs) and abbreviated new drug applications (ANDAs) with information on the appropriate regulatory classification of pharmaceutical co-crystal solid-state forms.[2] This guidance also provides information about the data that applicants should submit to support the appropriate classification of a co-crystal as well as the regulatory implications of the classification.

The recommendations in this guidance apply to materials that the Agency has not previously evaluated and determined to be pharmaceutical co-crystals. The recommendations do not apply to materials that the Agency has previously designated as salts, complexes, or other non-co-crystalline forms.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

09.11.2005. Further, the said document is a regulatory document and has nothing to do with patents or patentability requirements. The US FDA documents is a guidance document for classification of new drug applications submitted at the USFDA (*relevant extract*).

The Applicant further submitted that in the context of present invention, the supramolecular compound contains two active pharmaceutical ingredients, **Valsartan and Sacubitril, that are linked together by 'ionic interaction**'.

However, the 'co-crystal' as defined in the US FDA guidance documents composed active pharmaceutical ingredient (API) and **co-crystal formers ("coformers")**. Further, in 'co-crystal', the components that co-exist in the co-crystal lattice with a defined **stoichiometry interact non-ionically.**

GLOSSARY

Co-crystals: Crystalline materials composed of two or more different molecules, one of which is the API, in a defined stoichiometric ratio within the same crystal lattice that are associated by nonionic and noncovalent bonds.

Coformer: A component that interacts nonionically with the API in the crystal lattice, that is not a solvent (including water), and is typically nonvolatile.

Therefore, the argument of **Opponent 2 / Dr Dandala is not relevant for the purpose of present invention.**

SECTION 25(1)(H)

Section 8 :

The opponent no 8 submitted that *the patent applicant has failed to comply with its obligation to keep the Ld. Controller informed in writing of the the particulars of its foreign applications such as those prosecuted by it in China and Peru. The applicant has willfully suppressed the details of invalidation proceeding of the corresponding patent in China (application no. 200680001733.0), wherein an invalidation action was filed in November 2019 and a decision came in June 2021. While the decision was in favour of patent applicant, it is not absolved of the duty to disclose under the same under S. 8(1). Similarly, the patent applicant did not inform about the opposition proceedings against corresponding Peruvian patent application, which was initiated December 2007 with a decision being issued in October 2019.*

The opponent no 8 aruged that *the legislative history of S. 8 would show that S. 8(1) and S. 8(2) complement on another – S. 8(1) was intended to provide the substratum to the Patent Office from which the Patent Office could decide/determine the nature of information/documents that could be sought under S. 8(2). Here, in this case, by failing to disclose the existence of such invalidation and/oor opposition proceeding under S. 8(1), the patent applicant denied the Patent Office relevant information under S. 8(1) and the opportunity to exercise its mind to call for those records under S. 8(2). Such willful suppression of information relating to its corresponding foreign applications demonstrates the patent applicant's mala fides and constitute an egregious breach of S. 8(1), thus making out a case under S. 25(1)(h).*

The applicant submitted that the requirement of Section 8(2) is with respect to 'pending application' where examination has been initiated or continued. This is further supported by Rule 12(3) of the

Indian Patent Rules 2006, "when so required by the Controller under sub-section (2) of section 8, the applicant shall furnish information relating to objections, if any, in respect of novelty and patentability of the invention and any other particulars as the Controller may require which may include **claims of application allowed** within six months from the date of such communication by the Controller" [Rule 12(3)]

Thus, the law on Section 8(2) requires the Applicant to provide details of the proceeding of the examination of the application. Thus, once the patent has been granted against the foreign application, details pertaining to the post issuance proceedings are not required to be submitted.

The applicant submitted that the Applicant has complied with the requirement of Section 8.

a) Provided details of the corresponding application **20 times** on the following occasions. 17/12/2013; 23/05/2014; 16/06/2014; 12/01/2015; 29/05/2015; 18/11/2015; 07/12/2015; 28/04/2016; 01/11/2016; 28/02/2017; 10/04/2017; 01/11/2017; 28/03/2018; 20/09/2018; 22/03/2019; 24/10/2019, 02/04/2020; 08/09/2020; 08/03/2021; 10/05/2021; 11/05/2022 and 01/11/2022

b) Provided the information regarding search and examination report on multiple occasions along with allowed claims for the major countries. 26/05/2015; 27/07/2015; 4/08/2015; 07/12/2015; 28/02/2017; 10/05/2021

The applicant submitted that, there is more than sufficient compliance of Section 8(1) and 8(2). In this regard, reference has been m*ade to the following cases.*

a) Plead & Prove, Glaxo vs Kabi, 2013 order of the IPAB, Annexure 22.

b) Para 41, Delhi HC order in Communication components vs ACE Technology, Annexure 23.

c) Paras 101 and 103, Ericsson vs Intex, DHC, Annexure 24.

The applicant submitted that that the applicant has dutifully complied with all requirements under section 8(1) and 8(2). It is submitted the Applicant has discharged its duty and obligation under Section 8 of the Patents Act. Further, the application is still in the examination stage and the Applicant will provide any information as and when requested by the Learned Controller under Section 8(2).

Controller observation analysis and Conclusion

Analysis on Lack of Novelty

The opponent no 3 & 6 argued that the subject matter of claims of the present application which is drawn to a supramolecular complex of **valsartan and sacubitril** is anticipated by the disclosure of **WO'345 i.e. WO 2003/059345**.

The applicant argued that one of the main distinguishing feature of the present invention with respect to WO'345 is that the present invention is directed to **a single dual acting compound** whereas **WO '345 is**

directed to a composition comprising a combination of (a) AT-1 antagonist valsartan or a salt thereof, and (b) a NEP inhibitor, in particular (2R,4S)-5-biphenyl-4- yl-4-(3-carboxy-propionylamino)-2- methyl-pentanoic acid ethyl ester or a salt thereof. **The applicant further argued** that there is no reference whatsoever to a single dual-acting compound (unique novel compound) that combines two active ingredients by two different mode of action having an intricate network and stabilized by an involved network of ionic, hydrogen and coordination bonds, which has been described in various ways in the **IN'4412 specification**.

*The applicant argued that in **WO'345** :*

a) There is no reference to supramolecular compounds, complexes or cocrystals in WO'345.

*b) **Single Compound:** in the present invention valsartan and sacubitril are constituents of a single defined compound, whereas in WO'345 the chemical relationship between the individual active substances valsartan and sacubitril is left open..*

*c) **molar ratio is 1:1:** in the invention, valsartan and sacubitril are provided in the particular molar ratio of 1:1, whereas the ratios of valsartan andNEP inhibitor which may be administered are left open in WO'345 (see,for instance, WO'345, page 15, 2nd para).*

Controller conclusion :

After going through the submissions, arguments ,Expert Affidavits, Annexure and the documents acknowledged in the specification & cited by the opponents **,**it is clear that claims and specification of the Document WO'345 i.e. WO 2003/059345 does not describe a dual acting compound or supramolecular complex of two active agents having the same or different modes of action in one molecule. WO 2003/059345 describe a pharmaceutical composition comprising a combination of (i) the AT 1-antagonist valsartan or a pharmaceutically acceptable salt thereof and (ii) a NEP inhibitor or a pharmaceutically acceptable salt thereof and optionally a pharmaceutically acceptable carrier.
The controller agreed with the applicant arguments that the present claimed **novel and unique compound** is not a physical mixture of individual Na salts of **Valsartan and Sacubitril** but a compound that exhibited distinctly different spectral features in comparison to 1:1 mixture of the sodium salt ***(page 46, para 3 of the patent specification*)**.
Dr. Myerson also in **paras 2.1 to 2.10** of his **affidavit** refers to the present invention **as a "new / novel compound"**. **Dr. Motto** also in his affidavit at **para 19 and 22**, refers to the present invention as being "a **single compound"**. Also, experts of reputed scientific publications, ***Feng et al* refer to LCZ696** as a potentially **promising novel active ingredient** in pharmaceutical products.
It is not easily predictable, supramolecular compounds, complexes may or may not be formed. Apart from this, the properties of the synthesized supramolecular compounds, complexes cannot be anticipated ,the present invention relates to the supramolecular compounds, complexes could not be consider co-crystals , in the same class as that of salts or polymorphs. "
There is neither exemplification nor enabling disclosure of the claimed compound of the instant application in **WO'345**. In my view a person skilled in the art will not be able to synthesize claimed compounds in view of the disclosures and from the synthetic route provided in **WO'345**. The definitions of the various substituents in the prior art documents should be understood in the context of invention contained therein, examples, process for preparation and overall teachings of the document. An arbitrary selection is impossible without hindsight. None of the claims disclosed in WO'345 i.e. WO 2003/059345 fall within the scope of claim of the present invention as

amended. Accordingly, the compounds of the present claims are novel over WO'345 i.e. WO 2003/059345 and not anticipated in view of cited prior art documents.

I conclude that such a ground of opposition is not validly established by the any opponents.

Analysis on Prior claiming

The opponent no 8 (KETAKEE S. DURVE) argued that the Valsartan and Sacubitril supramolecular complex of the IN '4412 application has been already claimed in the earlier patent, (**D1: 1538/CHENP/2004 / IN229051). The opponent no 8 argued** that Section 25(1)(c) prevents double patenting and is often called the prior claiming objection. This ground of opposition is attracted if the subject application claims something already claimed in a specification filed in pursuance of a patent application in India, and this prior claim has an earlier priority date. **The opponent no 8 further argued** and cited **D1 or D1A** for the purpose of the present ground. **D1** is the Indian application of the same patent applicant, i.e., Novartis, with the earliest priority date of **17.01.2002. D1A** is the corresponding **PCT application** of D1 having the same priority date. In contrast, the subject application has a later priority date of **09.11.2005.**
The Opponent has relied on the following cases.
a) *Interactive Gift Express, Inc. Vs. Compuserve Incorporated* and Anr, United States Court of Appeals, Federal Circuit. (Jul 13, 2001); 256 F.3d 1323; 2001 WL792669 (*Annexure 9 filed by the Opponent*).
b) *Novartis AG & Ors vs Natco & Ors*, DHC order of Hon'ble Mr. Justice Jayant Nath, dated 28-Oct-2021 in C.S. (Comm) 62/2019 & Ors (*Annexure 10 filed by the Opponent*).
c) *AstraZeneca AB & Ors vs. Intas Pharmaceuticals & Ors in C.S. (Comm) 410/2020* by Hon'ble Justice Rajiv Shakdher *Annexure 11 filed by the Opponent*.
The applicant argued that "prior claiming under the provisions of the Indian Patents Act is contained in Section13(1)(b). The purpose of prior claiming is to ensure that one invention should be granted one patent (Section 46(2) of the Indian Patents Act).
The applicant draw attention to Rule 32 and Section 19(1) of the Indian Patent Rules as amended in 2006

The applicant argued that the **Opponent (KETAKEE S. DURVE)** has attempted to misguide the controller that patentability and infringement are two different concepts and issues. Infringement is an issue of violation of Patentee's rights conferred under **section 48,** whereas patentability is an issue involving novelty, inventive step and technical advancement under section 2(1)(j), 2(1) (ja), section 3, section 10 and section 13 of the Patents Act. Subsequent technical advancement, if it embodies or encompasses features of earlier patented invention, would infringe such earlier patent. Likewise, the fact that subsequent technical advancement infringes an earlier patent is not a ground for refusal of grant of patent nor is it a ground for opposition or revocation of a patent under section 25 and 64 of the Patents Act. This is also evident from reading of section 19 of the Patents Act, 1970. Reference may be made to: *Hindustan Lever vs. Lalit Wadhwa*, 2007 (35) PTC 377 (Del) (paras 14-16), enclosed as *Annexure 13*.

The applicant argued that the legal and technical arguments made by the Opponent by relying on the

concept of judicial estoppel as provided in *Interactive Gift Express, INC. VS. Compuserve Incorporated* case of the US Court of Appeals is misplaced and incorrect.

The applicant argued that the Opponent in order to invoke judicial estoppel relied on the decision of the ***Hon'ble Justice Jayant Nath in C.S. (Comm) 62/2019 (hereinafter referred to as 62/2019) dated October 28, 2021***. The Opponent is incorrectly reading the said decision and concept of judicial estoppel. The Patent Applicant/ Petitioner (in 62/2019) has not made any inconsistent pleadings and Opponent has misplaced and misconceived Patent Applicant's averments before the Court

Conclusion :

The controller agreed from the applicant arguments that **IN 229051** is basic patent where the Applicant for the first time claimed an invention for a combination of Valsartan or a pharmaceutically acceptable salt and Sacubitril or a pharmaceutically acceptable salt.
Controller observed that D1 is the patent for a combination of valsartan and sacubitril in a pharmaceutical composition and the scope of the both applications is different , Nowhere in the **D1** application is the super molecular complex mentioned. It is not reasonable in itself to consider the pharmaceutical composition of valsartan and sacbitril as a supramolecular complex of D1.
The Controller concluded that the findings made by the opponent with regard to Section 13 of the Act for the present patent application is not sustainable. The Applicant was only required to prove that the subject matter claimed in IN'4412 was different from the subject matter claimed in cited **D1 or D1A** for the purpose of the present ground, did not have to be proved to overcome the ground of anticipation by prior claiming.

I conclude that such a ground of opposition is not validly established by the any opponents.

Analysis on Obviousness/lack of inventive step

The documents relied by the opponents are listed below:

a) Document 1: WO2003/059345
b) Document 2: US5217996
c) Document 3 :WO2002006253
d) Document 4: EP0443983
l) Document 12:CN1443176
j) Document 10: WO2004/078163
e) Document 5: Packer et. al.,
f) Document 6: Morissette et. al.,
g) Document 7: Almarsson et. al.,
h) Document 8: Vishweshwar et. al.,
i) Document 9: Etter et. al.,
k) Document 11: Aakeroy et. al.,

The opponent no 2 (Natco Pharma) submiteed that the objections filed in respect of the filing of the Expert Affidavits, the Opponent would like to refer to the expert affidavits in support of the alleged invention to bring forth the contradictions in the statements of the Experts and that of the invention claimed. **The opponent no 2** surther submitted that the drug product of the compound, LCZ696 is a specific form and contains 2.5 degrees of hydration. Thus, the anydrate form which is claimed in the impugned patent admittedly unacceptable and less desirable. The entire evidence of Dr Motto is based on

discovery of an unusual compound - LCZ969 which is a specific crystalline, supramolecular complex. He in fact emphasizes on the fact how multiple rounds of experimentations were required and the other forms were not found to be stable and not desired.

The oppoenet no 2(Natco Pharma) argued that it is imperative that while the compound as recited in claim 1 can comprise 0-3 molecules of H20, in other words the compound can be both anhydrate and hydrate, the Applicant's claims thus encompassing anhydrate forms as well – no clarity if such forms would have the same properties as the hemipentahydrate.

.**The opponent no 2 submitted** that In this context reference is made to the pleadings from the Reply Statement and opinion of the inventor, Dr Piotr H. Karpenski which has been relied upon by Dr. Dhandla in his affidavit filed on August 9, 2022 -

(1) Document : WO2003/059345/ 1538/CHENP/2004 (D1)

The opponent no 2 (Natco Pharma) submitted that **WO2003/059345** at page 2 discloses that, "the nature of hypertensive vascular diseases is multifactorial. Under certain circumstances, drugs with different mechanisms of action have been combined. However, just considering any combination of drugs having different mode of action does not necessarily lead to combinations with advantageous effects. Accordingly, there is a need for more efficacious combination therapy which has less deleterious side effects." Thus, the problem solved by both D1 and the alleged invention is the same.

WO2003/059345 specifically discloses about the combination *((S)-N-valeryl-N-{[2'-(1H-tetrazole-5-yl)-biphenyl-4-yl]-methyl}-valine) and ((2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester. (Page 9).*

WO2003/059345 discloses that, **"***The compounds to be combined can be present as pharmaceutically acceptable salts. If these compounds have, for example, at least one basic center, they can form acid addition salts. Corresponding acid addition salts can also be formed having, if desired, an additionally present basic center. The compounds having at least one acid group (for example COOH) can also form salts with bases. Corresponding internal salts may furthermore be formed, if a compound comprises e.g. both a carboxy and an amino group.***"** *(Page 6)*

WO2003/059345 discloses that for N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4- amino-2R-methylbutanoic acid ethyl ester, preferred salts include the **sodium salt** disclosed in U.S. Patent No. 5,217,996. **WO2003/059345** D1 discloses further salts that may be formed. *(Page 6)*

DOCA test (pages 9 to 12)

In combination, **lower dosages of each agent are used and correspondingly,** valsartan is given in the range of 1 to 30 mg/kg/day and N-(3-carboxy-1 - oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester in dosages below 50 mg/kg/day. However, in cases wherein the responder rate is increased with combination treatment, the dosages are identical to those used as monotherapy. ***The available results indicate an unexpected therapeutic effect of a combination according to the invention.*** *(Page 12)*

In this composition, components (i) and (ii) can be obtained and administered together, one after the other or separately **in one combined unit dose form** or in two separate unit dose forms. The unit dose form may also be a fixed combination. *(Page 13)*

THEREFORE, D1 DISCLOSES PHARMACEUTICAL COMBINATIONS comprising VALSARTAN (or pharmaceutically acceptable salts) and SACUBITRIL (or a pharmaceutically effective salts thereof) optionally in the presence of a pharmaceutically acceptable carrier and pharmaceutical compositions comprising them.

VALSARTAN and SACUBITRIL administered together, one after the other or separately in ONE COMBINED UNIT DOSE FORM or in twoseparate unit dose forms. The unit dose form may also BE A FIXED COMBINATION. [page 13 of D1] VALSARTAN AND SACUBITRIL IN COMBINATION results indicate AN UNEXPECTED THERAPEUTIC EFFECT of the combination according to the invention.

The opponent 4 (Dr. Reddy's Laboratories Ltd.) argued that **D1 (WO 2003/059345** – granted in **India as IN 229051**; expiring on 16/01/2023) is directed to a pharmaceutical composition comprising a combination of (i) the AT1-antagonist valsartan or a pharmaceutically acceptable salt thereof and (ii) a NEP inhibitor or a pharmaceutically acceptable salt thereof and optionally a pharmaceutically acceptable carrier. D1 teaches that NEP inhibitor is preferably N-(3- carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester being sacubitril or a pharmaceutically acceptable salt thereof; and that the preferred salt of sacubitril is sodium salt. D1 also discloses that the combination of valsartan and sacubitril achieves better therapeutic effect than administration of valsartan alone or sacubitril alone.

The opponent 3 &6 (Kumar Sushobhan & G. Sriniwas Rao) submitted that WO2003/059345 relates to a pharmaceutical composition comprising a combination of (i) the AT 1- antagonist **valsartan or a pharmaceutically acceptable salt thereof** and (ii) a **NEP inhibitor or a pharmaceutically acceptable salt thereof** and optionally a pharmaceutically acceptable carrier and to a method for the treatment or prevention of a condition or disease selected from the group consisting of **hypertension, heart failure such as (acute and chronic) congestive heart failure, left ventricular dysfunction and hypertrophic cardiomyopathy,** etc .

The opponent 3 and 6 submitted argued that NEP inhibitors**, Sacubitril (N-(3-carboxy-1-oxopropyl)-(4S)-p-phenylphenylmethyl)-4-amino-2R-methylbutanoic acid ethyl ester),** has been discussed specifically in second last paragraph on page 6 and in in-vivo studies on page 9 to 12, and in claims . The invention of **WO345 pertains to and claims a composition of Valsartan and Sacubitril**, which are to be **administered together** or sequentially or simultaneously

The opponent 8 (KETAKEE S. DURVE) submitted that the claims of **D1A**(**WO2003/059345)**, demonstrating that a product comprising both valsartan and sacubitril is specifically claimed in these prior art documents. Therefore, the combined use of valsartan and sacubitril is clearly taught/disclosed in **D1A WO2003/059345**. While this is not disputed by the patent applicant in its reply, out of abundant caution, reference may be had to:

(a) Internal page 3, which discloses valsartan;

(b) internal page 3, which teaches the combined use of valsartan along with the NEP inhibitor;

(c) internal page 5, lines 1-5 of D1A, which discloses sacubitril as the preferred NEP inhibitor, as well as claim 3 of D1A that also lists sacubitril as a preferred NEP inhibitor;

(d) Claim 1 and claim 3 of D1A

The opponent 8 argued that Sacubitril is not sold separately as a drug; from **D1A**(**WO2003/059345)**, the combination of valsartan and sacubitril (or their respective salts) is known. It is not as if the format of ingestion, i.e., whether as two separate chemical compounds in one physical carrier versus the tow compounds put together in a single molecule as a complex, has any relevance to the mechanism of action of the molecules *in vivo*.

The opponent 8 argued the complex claimed in the subject application is the pro-drug for the composition disclosed and claimed in D1A.

The opponent 8(KETAKEE S. DURVE) D1A(**WO2003/059345)**, expressly also teaches the purported benefits of combining valsartan and sacubitril. Internal page 7, paragraph 3 to internal page 8, paragraph 2 teaches the person skilled in the art that putting these two compounds together achieves greater therapeutic effect than using them singly. Internal page 9 and internal page 11 also refer to animal testing for a combination of valsartan and sacubitril.

The applicant argued that the specifications of **IN '4412 and WO'345 (D1)** are neither similar nor identical to each other as they both relate to two separate inventions. There is no disclosure or even a

reference of the invention of including the claimed compound of IN'4412 anywhere in **WO2003/059345**. Second, the **Applicant submits** that by reading some lines from IN'4412 application so as to draw a comparison with D1 is false and read out of context. There is no similarity in D1 and IN'4412 as both D1 and IN'4412 relate to two separate inventions.

The applicant argued that **WO'345 discloses** a pharmaceutical composition comprising a **combination** of Valsartan and Sacubitril (*acknowledged by Dr. Ramesh Dandala inpara 13 of affidavit*). However, the subject matter of the IN'4412 application differs from the subject matter in WO'345 in at least the following respects
:

a) **Intricate network** in which anionic Valsartan, anionic Sacubitril, Sodium cation and water molecules interact in a network of ionic, hydrogen and coordinationbonds.

b) **Molar ratio is 1:1:** In the invention, Valsartan and Sacubitril are provided in molar ratio of 1:1, whereas the ratios of Valsartan and NEP inhibitor which may be administered are left open in WO'345 *(see, for instance, WO'345, page 15, second §).*

c) **Administration together:** in the invention, Valsartan and Sacubitril are provided in a form that necessitates their administration together, whereas in WO '345 the physical relationship of the individual active substances Valsartan and Sacubitril is left open *(see, for instance, WO '345, page 13, second* §) and

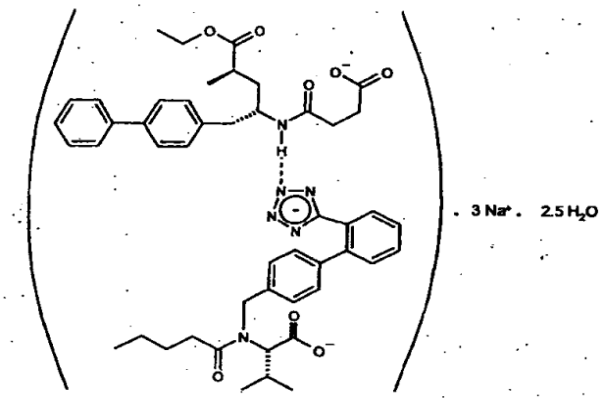
d) **Single Compound:** Valsartan and Sacubitril are constituents of a single defined compound – a trisodium compound, which may contain 0-3 water molecules, preferably a trisodium hemipentahydrate compound - whereas in **WO'345** the chemical relationship between the individual active substances Valsartan and Sacubitril is left open *(**para 4.4 of Dr. Myerson's affidavit**).*

The applicant argued that there is no teaching in **WO'345** towards dual-acting compound (unique novel compound) that combines two active ingredients with two different modes of action having an intricate network and stabilized by an involved network of ionic, hydrogen and coordination bonds.

The applicant argued that **IN'4412** application relates to a **supramolecular compound** comprising two active ingredients/ moieties (a) an angiotensin receptor blocker (Valsartan), (b) neutral endopeptidase inhibitor (Sacubitril) and sodium cations in a precise stoichiometric ratio, preferably 1:1:3. The compound may optionally further contain water molecules and has a hydration state defined in the claims by "x", which is 0-3 in claim 1, such as 0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 1, 2.25, 2.5, 2.75, or 3 (*p. 22 second to last paragraph and p. 23*). **The compound is a single entity that is stabilized by non-covalent interactions (including hydrogen bonds, ionic bonds and van der Waals forces).**
The preferred embodiment in the **IN '4412** is wherein "x" is 2.5, i.e., a hemipentahydrate and *(p. 22, second to last paragraph, of the specification of the 4412 Application*) is specifically claimed by claims 2 and 3 of the present application. The said embodiment is trisodium [3-((1S,3R)-1-biphenyl-4-ylmethyl-3-

ethoxycarbonyl-1- butylcarbamoyl)propionate-(S)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5-ylate)biphenyl- 4'-ylmethyl}amino)butyrate]-hemipentahydrate.
This preferred embodiment is exemplified in Examples 1-3 of the IN '4412 Application *(pages 40-43 of the specification)* and is fully characterized by various analytical and spectroscopic techniques *(p. 24-29 and 43-45 of the specification).* The therapeutic effect of the claimed compound has been confirmed in the representative animal studies performed and described in the specification of the IN '4412 Application (*p. 33-35 and paras 2.1 to 2.11 of Dr. Myerson's affidavit).*

b) A simplified structure of the said embodiment is shown below *(p.23 of the specification):*



The unique structural feature of the preferred embodiment of the present invention: The aforementioned preferred embodiment is a representative compound of the claimed invention known as LCZ696. Crystalline LCZ696 (referred to herein as "LCZ696") is unique with a complex interaction of ionic and hydrogen bonding between Valsartan anions, Sacubitril anions, sodium cations and water.

The asymmetric unit of the crystalline supramolecular complex consists of:
a) 6 molecules of Valsartan in its anionic form; b) 6 molecules of Sacubitril in its anionic form; c) 18 sodium cations;

d) 15 water molecules;

e) Monoclinic unit;

f) molecular formula of **$C_{288}H_{330}N_{36}O_{48}Na_{18}$•$15H_2O$ (M.W. 5748.03);**

g) The sodium cations are coordinated by oxygen ligands derived from **twelve carboxylate groups** and **eighteen carbonyl groups** (in the Sacubitril anions and Valsartan anions), and from 13 of the 15 water molecules (*see page 29, 3rd para of the patent specification* of IN'4412 application). The interactions are defined in the specification wherein the sodium cations are preferably coordinated to several oxygen ligands which come from carbonyl and carboxylate groups (*page 11, para 3 of the complete specification*).

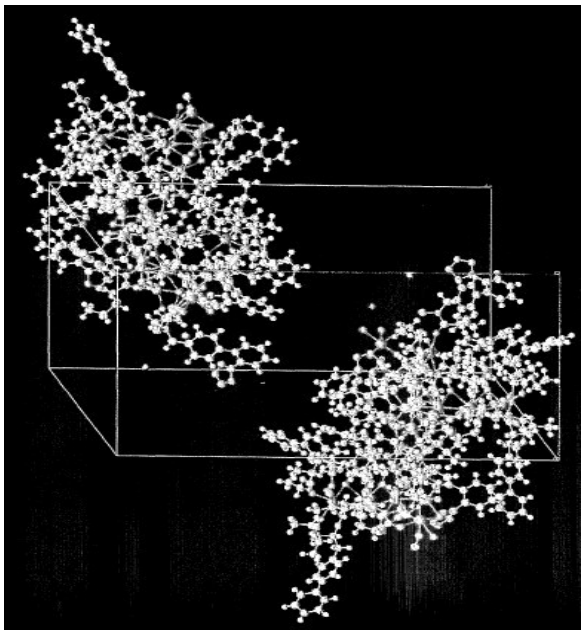
h) In all six of the Valsartan moieties, the tetrazole rings do not have an ionic bond directly to sodium, but instead form a hydrogen bond to the amide NH of the Sacubitril moieties; the amide carbonyl groups coordinate to the sodium ions. In addition, the tetrazole ring forms hydrogen bonds with water, which in turn forms part of the coordination polyhedra of the sodium ions. *(Feng et al., Fig.2).*

i) This **arrangement of sodium coordination is so efficient that each carbonyl and carboxy oxygen in both components is associated with multiple sodium ions**.

(Refer to "interactions" as described in the specification and the Feng article submitted with affidavits of Dr. Allan S. Myerson & Dr. Michael Motto on June 6, 2020) as well as the patent specification of the IN'4412 Application@ page 24 and 29)

j) This interaction leads to an association that makes the compound distinct from a combination of ARB and NEPi obtained by simply physically mixing the two active agents. Thus, the compound has different physico-chemical properties that make it particularly useful for manufacturing and therapeutic

The single crystal X-ray diffraction (SCXRD) data for the exemplified embodiment LCZ 696 of the claimed supramolecular compound reveal a highly unusual and intricate three-dimensional structure, *as summarized on page 28 of the specification of the 4412 Application.* A pictorial representation of the unit cell of the exemplified supramolecular compound, LCZ 696 comprising two asymmetric units is represented in *Fig. 1 of the IN 4412 Application*, and reproduced below:



Pictorial representation of the unit cell of LCZ696 *(page 29, paras 2-3 of the complete specification of the IN'4412 Application)*

Controller Conclusion on (WO2003059345) : After listening to the arguments of the opponents and the applicant, it is observed that the present invention is directed to "*a dual acting compound or supramolecular complex of two active agents having the same or different modes of action in one molecule."* while the cited document is **WO2003059345** a pharmaceutical composition comprising (i) the AT 1 -antagonist valsartan or a pharmaceutically acceptable salt thereof and (ii) a NEP inhibitor or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier. Nowhere in **WO2003059345** has the information about the Supra molecular complex been given. There is no teaching in WO '345 that would have
prompted a person skilled in the art to arrive at the claimed supramolecular compound of Valsartan and Sacubitril .The controller agreed from the applicants arguments that the compound patent differs from the WO '345 . The distinguishing features between the claimed subject-matter and **WO2003059345 is that the present invention** in the **IN '4412** application both valsartan and sacubitril in a single compound comprising of both active ingredients in a ratio which turned out to be the desired precise stoichiometry at a fixed 1:1 molar ratio, is a **significant advantage**. **Novel single compound** comprising in which entities Valsartan and Sacubitril are present in 1:1 stoichiometric ratio (*Dr. Motto's evidence*) whereas in **WO'345** , **there is no reference to supramolecular compounds, complexes in WO'345**.
In the present invention valsartan and sacubitril are constituents of a single defined compound, whereas in **WO'345** the chemical relationship between the individual active substances valsartan and sacubitril is left open which is in the composition.In the present **IN '4412** invention invention, valsartan and sacubitril are provided in the particular molar ratio of 1:1, whereas the ratios of valsartan and NEP inhibitor which may be administered are left open in.**It is concluded that** Nowhere does the illustrative claims and specification of **WO2003059345** provide any information on the teaching of the present invention **IN '4412**. Therefore the present invention is completely non-obvious over the cited prior art **WO2003059345.**

(2) Document : **US5217996(D2) :**

The opponent no 2 (Natco Pharma) submitted US5217996 discloses the specific NEPi inhibitor and the sodium salt thereof isexemplified. N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-2Rmethylbutanoic acid ethyl ester and is specifically disclosed and
Sodium N-(4-carboxy-1-oxobutyl)-(4S)-p-phenylphenylmethyl-4-amino-2R methylbutanoic acid ethyl ester, melting at 68°-72° C are specifically exemplified and disclosed. *(Column 21 lines 66 to 68 and column 22 example 4)*
The opponent no 4 (Dr. Reddy's Laboratories Ltd.) submitted US 5217996 discloses the compound which acts as NEP inhibitor and which can be used as antihypertensive saluretic agents, and specifically in the examples 7 and 8 and claim 6, teaches the sodium salt of the sacubitril [N-(3- Carboxy-1-oxopropyl) -(4S)-p-phenyl phenyl methyl)-4-amino2R-methyl butanoic acid, ethyl ester

The opponent 3 &6 (Kumar Sushobhan & G. Sriniwas Rao) submitted US5217996 (US'996) discloses NEP inhibitors including Sacubitril, N-(3-carboxy-1-oxopropyl)-4-(p-phenylphenylmethyl)-4-amino-2-methylbutanoic acid ethyl ester. **The only salt form exemplified for the NEP inhibitors discloses therein including Sacubitril is the sodium salt form** [Please refer Examples 3 to 6].
The opponent no 3 and 6 argued that US5217996 teaches a person skilled in the art that Sacubitril which is one of the NEP inhibitors disclosed can be converted into its metal salt such sodium salt by reacting it with equivalent amount of corresponding base i.e. if sodium sacubitril has to be prepared it should be reacted with NaOH in equivalent amounts. The process of the impugned application also discloses reaction of the free acid i.e. the APIs sacubitril and valsartan to be reacted with corresponding base i.e. NaOH (sodium hydroxide) in order to form sodium salt.

The applicant submitted that US5217996 (US '996) discloses neutral endopeptidase inhibitors, in particular Sacubitril and its sodium salt, and. Further, the IN '4412 application referred to both, US '996 and EP '983 in the patent specification. Example 8 of US '996 discloses preparation of sodium salt of Sacubitril capsules containing 50 mg of [N-(3-Carboxy-1-oxopropyl)-(4S)-p-phenyl phenyl methyl)-4-amino-2R-methyl butanoic acid, ethyl ester].
The applicant argued that there is no reference of any combination of valsartan with sacubitril in **US '996** let alone the compound claimed in the IN '4412 application. It is irrelevant that **US'996** discloses a sodium salt of sacubitril because the claimed compound is not a mere physical mixture of sodium salts of valsartan and sacubitril – it is a new and unique single compound. US'996 therefore provides no relevant teaching towards the invention.

The applicant further argued that In any event, that sodium salt of sacubitril is not good for further development as the said salt of sacubitril is hygroscopic as **shown below and also presented as Annexure B**

PROPERTY	LCZ696	VALSARTAN DISODIUM SALT	SACUBITRIL MONOSODIUM SALT
HYDRATION	2.5 H_2O	3 H_2O	ANHYDROUS
HYGROSCOPICITY (% AT 60% RELATIVE HUMIDITY)	0.6	5	13
HYGROSCOPICITY (% AT 75% RELATIVE HUMIDITY)	6.9	6.5	26

The amount of absorbed moisture in a drug can influence the **flow and compression characteristics of powders** during manufacture and can have an impact on the hardness of final tablets and granulations. Water absorption by APIs also frequently **affects the physical and/or chemical stability of final dosage** forms and always introduces serious content uniformity concerns. **This again will not motivate person skilled in the arts to use monosodium salt of Sacubitril and there is a clear teaching away.**

Controller Conclusion on (US5217996) (D2)

The Document US5217996 focuses on the problems associated with the neutral endopeptidase inhibitors, in particular Sacubitril and its sodium salt, On the other hand, the instant Application **IN '4412** discloses a "**dual-acting compound", i.e. a single compound** that has two different modes of action, namely angiotensin receptor blockade (ARB) resulting from valsartan and NEP inhibition resulting from sacubitril .The reference to "**supramolecular complex"** in the patent specification has been used by the Applicant to define the **interaction** between the two pharmaceutically active agents, cations and any other entity present by means of non-covalent intermolecular bonding between them.The Document **US5217996** is completely silent on any **dual-acting compound", i.e. a single compound** that has two different modes of action disclosed therein . **US'996** discloses a sodium salt of sacubitril because the

claimed compound is not a mere physical mixture of sodium salts of valsartan and sacubitril – it is a new and unique single compound.
Therefore, the problem and solution focused by the Document **US5217996** and the instant Application is entirely different. Therefore. a person skilled in the art trying to achieve the objectives of the claimed invention will never consider the Document **US5217996** as a relevant piece of art. Thus, the claimed invention is therefore inventive over the Document **US5217996**.

(3) Document : **WO2002006253(D3)**

The opponent no 2 (Natco Pharma) submitted that **WO2002006253** discloses about valsartan and the mono-sodium and disodium salt and hydrate thereof (**Example 5, 10 and page 3**) *The active ingredient valsartan is the free acid which is described specifically in EP 0443983, especially in example 16; it has two acidic hydrogen atoms: (i) the hydrogen atom (H atom) of the carboxyl group, and (ii) that of the tetrazole ring. Accordingly, one acidic H atom (primarily the carboxyl H atom) or both acidic H atoms may be replaced by a monovalent or higher valent, e.g. divalent, cation. Mixed salts may also be formed. (page 1).*
The opponent no 2 (Natco Pharma) argued preferred salts are for example selected from the mono-sodium salt in amorphous form; di-sodium salt of valsartan in amorphous or crystalline form, especially in hydrate form, thereof. (Page 3) Compared with the free acid, the salts according to the invention, or the amorphous forms, solvates such as salt hydrates, and also the corresponding polymorphous forms thereof, have unexpectedly advantageous properties. (**Paragraph bridging pages 3 and 4)**
The opponent no 2 (Natco Pharma) argued WO2002006253 teaches that Valsartan and its salts by itself and in combination with NEPi for the treatment of congestive heart failure.

The opponent no 4 (Dr. Reddy's Laboratories Ltd.) submitted WO 02/06253 relates to new salts of valsartan or crystalline, also partly crystalline and amorphous salts of valsartan, the respective production and usage, and pharmaceutical preparations containing such a salt. It is submitted that **WO 02/06253** specifically intends to meet the need in the art for more stable crystalline forms of valsartan and teaches towards salts of valsartan which are selected from the group consisting of the monosodium salt, the disodium salt, the monopotassium salt, the dipotassium salt, the magnesium salt, the calcium salt, the bis-diethylammonium salt, the bis-dipropylammonium salt, the bis-dibutylammonium salt, the mono-L-arginine salt, the bis-L-arginine salt, the mono-L-lysine salt and the bis-L-lysine salt, as well as salt mixtures, or respectively, an amorphous form, a solvate, especially hydrate, as well as a polymorphous form thereof, the respective production and usage, and pharmaceutical preparations containing such salts.

The opponent 3 &6 (Kumar Sushobhan & G. Sriniwas Rao) submitted that WO253 explicitly teaches that the hydrate salt form of Valsartan such as disodium Valsartan hemihydrate has better solubility and bioavailability than the free acid Valsartan. Since it was known in art that salt hydrate form of Valsartan has higher bioavailability as compared to free acid form of Valsartan, it is implied that for achieving similar level of bioavailability, the required amount of salt hydrate form of Valsartan will be lesser than the required amount of free acid form of Valsartan .

The opponent 3 &6 (Kumar Sushobhan & G. Sriniwas Rao) submitted WO253 teaches that the crystalline salt forms, especially crystalline salt hydrates of Valsartan have numerous advantages over Valsartan free acid which includes better water solubility, higher stability, higher bioavailability, no water absorption or water loss on keeping (i.e. much less or no hygroscopicity), betterstability. Therefore, a person skilled in the art is taught to use **Valsartan crystalline salt hydrate form over Valsartan free acid** .

The applicant argued that the claimed compound is a new single compound and is distinct (separately patentable) from a mere physical mixture of sodium salts of valsartan and sacubitril. **WO'253**, which relates to simple salts of valsartan, provides no relevant teaching towards the invention. In any event, Valsartan, in an approved form (Diovan & Co-Diovan) is present as free acid, i.e. not as a salt, and this wellknown free acid form would have been the obvious route for the skilled person looking to develop valsartan.

The applicant further argued that **WO '253** provides a laundry list of salts of valsartan. However, a person skilled in the art will read this document as a whole and upon reading the document recognize that calcium tetrahydrate and magnesium hexahydrate are "particularly preferred" due to their "exceptional physical stability" (*page 4, middle §; page 6, 5th paragraph; also other "outstanding" properties on pages 7, 15 and 23*). ***WO '253*** *at pages 7, 15 & 23* clearly reports that the said two salts have water solubility several times better than that free acid of valsartan, have high melting point and excellent chemical and physical stability and is suitable for pressing directly to form corresponding tablet formulation and has advantageous properties such as uniform crystal conglomerates which can be used in the galenic formulation.

The applicant argued that no such advantageous properties are attached to sodium salt – to the contrary Na salt has poor physical properties.
a) Example 5 (page 47) describes disodium valsartan as "hygroscopic".
b) Example 11 (page 51) describes a disodium valsartan hydrate which is "slightly hygroscopic" and ill-defined stoichiometry (2.4 ± 1.0 moles).
The applicant further argued , a person skilled in the art would be motivated to use the calcium/magnesium salt of valsartan and not the disodium salt particularly when the said disodium hydrate salt of valsartan is hygroscopic (*pages 47 & 52, §1*). Further, the formulation example 1 and 2 disclosed in WO 253 at pages 59 and 60 provide a tablet with calcium tetrahydrate and magnesium hexahydrate.
The applicant further argued that **Dr. Motto states (para 17)** that during the research the inventors recognized that to form double salt with monovalent cations seemed scientifically non-viable and counter intuitive and therefore a person skilled in the Arts would not have developed a sodium salt of valsartan. (P.S Valsartan is a diprotic acid and therefore it was clearly a teaching away to use a monovalent salt (Na, K) instead of a divalent salt (Ca or Mg). Therefore, POSA would be motivated to use calcium tetrahydrate and magnesium hexahydrate and will be taught away from using a monovalent salt such as a sodium salt of valsartan. This is notwithstanding the fact that in the present invention, the compound is not a salt of valsartan (*See page 46 of the patent specification also)*

Controller Conclusion on (WO2002006253 D3) :The Document WO2002006253 discloses new salts of valsartan or crystalline, also partly crystalline and amorphous salts of valsartan, the respective production and usage, and pharmaceutical preparations containing such a salt. **It is observed the Document WO2002006253** describes a disodium hydrate salt of valsartan which is "hygroscopic" and example 11 describes a disodium hydrate salt of valsartan whichis "slightly hygroscopic" and having an ill-defined stoichiometry (2.4 ± 1.0 mole H2O). **High hygroscopicity and ill-defined stoichiometry** are properties that frequently lead to difficulties in formulation and manufacture of pharmaceuticals. The present invention **IN 4412 discloses** a new single compound and is distinct from a mere physical mixture of sodium salts of valsartan and sacubitril . The IN '4412 application provides the effects of both valsartan and sacubitril in a single compound . There is no reference whatsoever to a single dual-acting compound (unique novel compound) that combines two active ingredients by two different mode of action having an intricate network and stabilized by an involved network of ionic, hydrogen and

coordination bonds, which has been described in various ways in the IN'4412 specification. Therefore, a person skilled in the art trying to achieve the objectives of the claimed invention will never consider the Document **WO2002006253** as relevant piece of art. In view of the above, the claimed invention is inventive over the Document **WO2002006253**.

(4) <u>Document EP0443983 (D4):</u>

The opponent no 2 (Natco Pharma) argued that **EP0443983** discloses about valsartan and the mono-sodium and disodium salt and hydrate thereof (Example 5, 10 and page 3). The active ingredient valsartan is the free acid which is described specifically in **EP 0443983**, especially in example 16; it has two acidic hydrogen atoms: (i) the hydrogen atom (H atom) of the carboxyl group, and (ii) that of the tetrazole ring. Accordingly, one acidic H atom (primarily the carboxyl H atom) or both acidic H atoms may be replaced by a monovalent or higher valent, e.g. divalent, cation. Mixed salts may also be formed. (page 1).
The opponent no 2 argued that EP0443983 teaches Valsartan and its salts by itself and in combination with NEPi for the treatment of congestive heart failure.

The opponent no 4 (Dr. Reddy's Laboratories Ltd.) submitted that **EP0443983** discloses and claims valsartan for the first time. **The opponent no 4 (Dr. Reddy's Laboratories Ltd.) submitted** that the compound valsartan as disclosed in the present prior art has the IUPAC name (S)-N-valeryl-N-{[2'-(1H-tetrazole-5-yl)- biphenyl-4-yl]-methyl}-valine.

The applicant argued that **EP '983** is acknowledged by the applicant in the patent specification of **IN ' 4412** at page 14. **EP '983** does not describe (nor suggest) to combination of valsartan and sacubitril let alone the novel dual acting compound claimed by the claims of **IN 4412.**

Controller Conclusion on (EP0443983) : EP0443983 discloses about valsartan and the mono-sodium and disodium salt and hydrate which is , the problem and solution focused by the Document **EP0443983** and the instant Application is entirely different.Therefore **IN 4412 is inventive over the cited document EP0443983.**

(5) <u>Document WO2004/078163(D5):</u>

WO2004/078163 discloses a pharmaceutical co-crystal composition, comprising: an API and a co-crystal former, wherein the API is a liquid or a solid at room temperature and the co-crystal former is a solid at room temperature, and wherein the API and co-crystal former are hydrogen bonded to each other.

The applicant argued that WO '163 discloses 'Pharmaceutical co-crystal compositions. Table IV list more than 3500 APIs including valsartan and more than 100 co-crystal formers. However:
a) There is no disclosure of any specific example for forming a co-crystal of valsartan with any of these co-crystal formers.
b) **WO '163** is just a research program and has no pointers to sacubitril, or the combination of sacubitril and valsartan.
c) **WO '163** discloses a long list of co-crystal formers, all of which are neutral molecules.
d) The co-crystals of **WO '163** are defined as comprising a co-crystal former. WO '163 does not teach that the co-crystal can be used to provide a combination therapy of two APIs. Rather, WO '163 mainly focuses on the co-crystal properties of the API (first API).

WO '163 teaches away from combining valsartan and sacubitril into a co-crystal, since sacubitril was not approved at the priority date by FDA or any other Health Authorities over the world, and thus was not proven to be safe for use in a pharmaceutical product.

Controller Conclusion on (WO2004/078163) : WO2004/078163 discloses 'Pharmaceutical co-crystal compositions in compairsion with IN4412 there is no disclosure of any specific example for forming a co-crystal of valsartan with any of these co-crystal formers. WO '163 **teaches away** from combining valsartan and sacubitril into a co-crystal, There is no teaching or suggestion in **WO2004/078163** to motivate a person skilled in the art to contemplate the provision of compounds that comprise a "**dual-acting compound", i.e. a single compound** that has two different modes of action, namely angiotensin receptor blockade (ARB) resulting from valsartan and NEP inhibition resulting from sacubitril. **Neither is there any teaching or suggestion** in **WO2004/078163** that to prepare a dual acting compound of the **IN '4412** application supramolecular compound comprising Valsartan and Sacubitril with features referred to in *paras 23-34* (about the invention) as well as elucidated in the patent specification. Therefore **IN 4412 is inventive over the cited document WO2004/078163 .**

(6) <u>Document CN1443176A (D6)</u>

During the hearing the opponent no 8 cited Chinese patent document **CN1443176A**, "Valsartan salts published on September 17, 2003.

The opponent no 8 (**KETAKEE S. DURVE**) **submitted** that **CN1443176A** teaches that there is a need for a more stable crystalline form of valsartan (paragraph 7), since such crystalline forms tend to have more advantageous properties (para 14-16). In this context, **CN1443176A** states that the object of the invention in **CN1443176A** is the preparation of a salt of valsartan selected from a specific group of salts, the 1st of which is sodium salt of valsartan (paragraph 9). In fact, **CN1443176A** goes a step further and states that sodium salts of valsartan, especially in hydrated form of the preferred salts (para 12). **CN1443176A** also states that the invention in that prior art relates to solvents and hydrates of such valsartan salts (para 19).

The Applicant argued that the claimed compound is a new single compound and is distinct (separately patentable) from a mere physical mixture of sodium salts of valsartan and sacubitril. **CN'176/WO'253** , which relates to simple salts of valsartan, provides no relevant teaching towards the present invention. In any event, valsartan, in an approved form (Diovan & Co-Diovan) is present as free acid, i.e. not as a salt, and this well-known free acid form would have been the obvious route for the person skilled in the art looking to develop valsartan. The Applicant submits that there is no reference of any combination of Valsartan with Sacubitril in WO '253 let alone the compound claimed in the IN '4412 application.

Non-Patent Literature

(Morissette et al. - High-throughput crystallization: polymorphs, salts, co-crystals and solvates of pharmaceutical solids)

The opponent no 2 (Natco Pharma) submiteed that Co-crystals of drugs and drug candidates represent a new type of material for pharmaceutical development. They are part of a broader family of multicomponent crystals that also includes salts, solvates, clathrates, inclusion crystals and hydrates as shown in **Scheme 2.** The primary difference between solvates and co-crystals is the physical state of the isolated pure components: if one component is a liquid at room temperature, the crystals are designated as solvates; if both components are solids at room temperature, the crystals are designated as co-crystals. While at first glance these differences may seem trivial, they have profound impact on preparation, stability and ultimately on the ability to develop products.
The opponent 2 (Natco Pharma) argued that in the present case, the doses of Valsartan and Sacubitril were well known in prior art including D1 and a skilled person can easily comprehend the stoichiometric ratios without any undue experimentation.
The opponent no 3 and 6 argued that Morissette and Christer teach that a co-former forms non-covalent bonds with the different molecules and gets incorporated via non-covalent bonds into the co-crystal as an integral part of the co-crystal. **The opponent no 3 and 6 submitted** that the sodium molecules and water molecules of the salt hydrate act as co-formers which form non-covalent bonds with Valsartan & Sacubitril and gets incorporated via non-covalent bonds into the co-crystal as an integral part of the co-crystal.

The opponent no 3 and 6 argued that prior art documents such as Morissette and Christer teach formation of several cocrystals, the mechanism of bonding in these co-crystals, as well as general scheme of synthesis of co-crystals. Said documents reveal that molecules and ions in solution interact with each other to form to neutralize each other's charges and that this interaction is by non-covalent bonds such as ionic bonds, hydrogen bonds, and van-der-waals forces resulting in a stable co-crystal .

The applicant argued that this article is of 2004, not long before the priority date of the present invention,Morissette is a review article on high-throughput crystallization that discusses engineering of single API co-crystal. Morissette's definition of co-crystals requires that at least one component is **nonionized** (*Scheme 2, page 293)* and a co-former. This will therefore exclude and **teach away** from the present compound as it has
a) Anionic Valsartan;
b) Anionic Sacubitril; and c) Cationic sodium
Morissette recognizes that the formation of pharmaceutical co-crystals involving ONE API and a co-former was unpredictable and not a matter of routine in drug development at the priority date (*page 276 RHS last para*).
The applicant argued that Morissette recognizes that despite centuries of research the fundamental mechanisms and molecular properties that drive crystal form diversity, specifically the nucleation of polymorphic forms, are **not well understood** and therefore **predictive methods** for

accessing behavior remains a **formidable challenge** [page 276, RHS, last para]. T**he prediction** of packing structures for multicomponent (e.g., solvates, hydrates, co-crystals) or ionic systems **is not yet possible** [page 277, LHS, first para].

The applicant further argued that article further recognizes at page 296 LHS) under the head "summary and outlook", that conducting extensive crystallizations with small amounts of material using a variety of solvents, additives and conditions necessarily generates large sets of data and the said information is of **limited value**. The article further demonstrates unpredictability in the art: The existence and identity of hydrates, solvates, co-crystals and polymorphs have **defied prediction** and that in general discrete crystal forms are considered **non-obvious and patentable**. *page 296 (RHS, last para)*

Almarsson et al.) (page 1889, pg 231 of REP

The opponent 2 (Natco Pharma) submitted that **D5 (Almarsson et al.)** discusses the evolution of crystal engineering into a form of supramolecular synthesis and the problems and opportunities in the pharmaceutical industry. It defines pharmaceutical co-crystals as being a subset of a broader group of multi-component crystals that also includes salts, solvates (pseudopolymorphs), clathrates, inclusion crystals and hydrates. In a supramolecular context, solvates and pharmaceutical co-crystals are related to one another in that at least two components of the crystal interact by hydrogen bonding and, possibly, other non-covalent interactions rather than by ion-pairing. **Page 1894 (pg 236 of REP).**

The applicant submitted that this article is of **2004**, not long before the priority date of the present invention and therefore, recognizes that the formation of co-crystals is at a **nascent/infancy stage.**

The applicant submitted that the said article does not teach towards using co crystals involving two API's as a **routine approach** for providing combination therapies.
The applicant submitted that Almarsson focusses on the design of co-crystals involving a single API and pharmaceutically inert co-former. [*Page 1894 (LHS)*].
a) **Co-crystals are not routine part of pharmaceutical research** Almarsson states that pharmaceutical co-crystals "represent a relatively **unexplored class of compounds**" *(p. 1890, page 1890, LHC, 1st paragraph and Para 4.20 of Myerson]*
b) **Co-crystal formation is of One API only and a co-former agent**: Almarsson discusses the design of single API cocrystals. It only speculatively suggests a possibility of using an API in **sub-therapeutic amounts** as a co-former (i.e. the co-former API is not used as therapeutic agent) and stresses that this idea is "provocative". (*page 1894, LHC, final few lines)*

The applicant argued that **Almarsson et al. , does not teach the use of a supramolecular compound containing two APIs in therapeutic amounts (i.e. a dual acting compound). To the contrary Almarsson teaches the use of inert co-former agents.**

The applicant argued that the allegation that Almarsson et. al. discloses natural tendency of acid and amide moiety to form a heterosynthon co-crystal as both Valsartan and Sacubitril have tetrazole/amide moiety is illogical for the following reasons:

a) The co-crystal formation is unpredictable and merely based simply on functional groups present cannot be predicted.

b) Valsartan and Sacubitril are ionized in the claimed compound and therefore do not contain any carboxylic acid group.

c) The presence of carboxylic acid and amide in Sacubitril would only lead to the conclusion that it contains **self-complementary groups** and thus could crystallize on its own (self-organization) in its free acid form. Similarly, Valsartan has a tetrazole and carboxylic acid moiety which would similarly indicate that Valsartan could crystallize on its own in its free acid form.

Vishweshwar et al. -Crystal engineering of pharmaceutical co-crystals from polymorphic active pharmaceutical ingredients (pg 239 of REP)

The opponent 2 (Natco Pharma) submitted that Vishweshwar et al. an article on crystal engineering of pharmaceutical co-crystals from polymorphic active pharmaceutical ingredients. Pharmaceutical co-crystals address physical property issues. The discussion involves as to how carboxylic acids and amides form hydrogen bonds and illustrated the co-crystals formed by Piracetam with a combination of gentisic acid and p-hydroxybenzoic acid. In column 2 , at page 4601 (239 of REP) it teaches that single crystals of 1:1 co-crystal of piracetam and gentisic acid were obtained via slow evaporation from. **The opponent 2 (Natco Pharma) argued** that **Vishweshwar et al.** teaches that co-crystals can be formed from grinding of slurrying in water. In page 4602 (pg 240 of REP) it discloses the various solvent which the solvents which were tested and used including acetone, water, methoanol, ethanol…."

The applicant submitted that the article **Vishweshwar et al.** is of July 2005, couple of months before the priority date of the present invention and therefore, recognizes that the formation of co-crystals is at a **nascent/infancy stage.** It describes the formation of a piracetam cocrystal with either gentisic acid or p-hydroxybenzoic acid, which are simple aromatic acids being used as co-formers not as therapeutic agents for combination therapy, i.e., one single API and co-former.

The applicant argued that Vishweshwar further recognizes that around the priority date co-crystals "**remain relatively unexplored"** (*page 4601*).
Vishweshwar has got nothing to do with valsartan, sacubitril or the compound. The formation of the simple compounds in Vishweshwar is not similar in any manner to the compound of the present invention. In fact, neither sacubitril nor valsartan have primary amide group. Moreover, the compound does not even have a carboxylic acid-primary amide heterosynthon as taught by Vishweshwar or any other carboxylic acid-amide heterosynthon.

Other Non-Patent Literature

Opponent 4 (Dr. Reddy's Laboratories Ltd.) submitted that Research Article titled as "Hydrogen-bond directed cocrystallization as a tool for designing acentric organic solids" by **Etter et al**. published in

January 1989, Chemistry of Materials, Vol 1 , 12 -14 . **The opponent no 4 submitted** that **Etter et al** teaches a process for preparing a 1:1 co-crystalline complex of 4-aminobenzoic acid (4- ABA) and 3,5-dinitrobenzoic acid (3,5-DNBA) via a hydrogen bonding.
Opponent 4 (Dr. Reddy's Laboratories Ltd.) submitted that the document **Etter et al** teaches co-crystallization of organic compounds. It is submitted that D2 teaches two methods of production of same co-crystal of two anions: (i) solution co-crystallization, and (ii) solid-state grinding, in as early as 1988, when the article was published. It is submitted, hence, that the methods of co-crystallization of the organic compounds are well known in the art and in fact common general knowledge for a practitioner in the field.

The applicant argued that **Etter et al.,** is a non-analogous art and cannot be used for inventive step analysis in view of **Pharmacyclics vs. Laurus Labs, IPAB order, 2020 in OA/46/2020/PT/DEL).** .
Etter et al., deals with optical materials and not pharmaceutical compounds.
The applicant argued that Etter et al., clearly states as follows (**Page 10, RHC**):
"Despite notable advances in understanding the molecular basis of organic crystal growth processes, **there are still no general synthetic tools available for controlling the structures of molecular aggregates** or crystals." Thus, there is no **general** teaching with respect to generating supramolecular (molecular aggregate) structures.

The applicant argued that Aakeroy et al., **'teaches away'** from creating a complex because their existence and formation are completely unpredictable.

Controller conclusion on Non-Patent Literature

The present patent application **IN4412** the applicant in their patent specification has defined "supramolecular complex" as an interaction between the two pharmaceutically active agents, cations and any other entity present by means of non-covalent intermolecular bonding between them The claimed compound of the IN '4412 application is a **new and unique single compound Morissette et. Al ., discloses in that** Morissette's definition of co-crystals requires that at least one component is **nonionized** (*Scheme 2, page 293)* and a co-former. This will therefore exclude and **teach away** from the present compound as it has a) Anionic Valsartan; b) Anionic Sacubitril; and c) Cationic sodium. The article further demonstrates unpredictability in the art: The existence and identity of hydrates, solvates, co-crystals and polymorphs have **defied prediction** and that in general discrete .
Almarsson et al., certainly does not teach the use of a supramolecular compound containing two APIs in therapeutic amounts (i.e. a dual acting compound). To the contrary Almarsson teaches the use of inert co-former agents. **Vishweshwar** has got nothing to do with valsartan, sacubitril or the compound. The formation of the simple compounds in Vishweshwar is not similar in any manner to the compound of the present invention. **Etter et al.,** there is no **general** teaching with respect to generating supramolecular (molecular aggregate) structures **Aakeroy et al**., **'teaches away'** from creating a complex because their existence and formation are completely unpredictable.

In this context, **it has been mentioned in the article** that published as "**A Review about Regulatory Status and Recent Patents of Pharmaceutical Co-Crystals** (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6156475/) by Arun Kumar, Sandeep Kumar, and Arun Nanda* Adv Pharm Bull. 2018 Aug; 8(3): 355–363. Published online 2018 Aug 29 ,which is is stated that ***co-crystal structure cannot be predicted from the available sources*** "**co-crystals well satisfy the Non-obviousness criteria"**

"Non-obviousness means that if someone skilled in the relevant field of technology and familiar with its subject matter invented it with comparative ease; such an "invention" would be novel but obvious to that person**.** Desiraju described that unlike salt formation wherein an acid is necessary to form a salt with a base, the identification of a co-former is hardly an ever routine. According to Trask, in spite of a number of co-crystals screening methods available, there is no confirmed way to predict whether two molecules will form a hydrogen bond and a co-crystal will be formed. ***There are a lot of factors that govern the co-crystallization process and still there is a need to better understanding of this process. Moreover, co-crystal structure cannot be predicted from the available sources. Hence co-crystals well satisfy the Non-obviousness criteria too."***

" Dr. Michael Motto's affidavit also highlights the difficulties and unpredictability to unite Sacubitril and Valsartan into a single chemical entity. Dr. Motto's affidavit clearly shows that it was **NOT a routine technique** to combine two active pharmaceutical ingredients ("APls") into a single compound at the priority date. There was simply no precedent or expectation at the priority date for the formation of a single compound comprising Valsartan or Sacubitril, let alone a single compound comprising both APls in the form of anions at the therapeutically desirable 1:1 molar ratio, together with sodium cations and optionally water molecules.

It is concluded that none of the cited reference Almarsson et al , Morissette et. al , Aakeroy et al , Vishweshwar et al ,Etter et al., and Other Non-Patent Literature discussed during the hearing alone or in combination "teach", "suggest" or "motivate" the subject-matter as claimed in the present invention and it is non-obvious for a person skilled in the art to arrive at the present invention. So that the subject-matter as claimed in the present invention is inventive over the cited documents.

Controller Coclusion on Obviousness/Lack of inventive step

I have gone through all the prior art documents, opposition petitions, replies and written note of arguments by the parties. During the arguments, and after interpretation of the prior arts **WO'345 discloses** a pharmaceutical composition comprising a **combination** of Valsartan and Sacubitril (*Dr. Ramesh Dandala in para 13 of affidavit*). However, the subject matter of the IN'4412 application differs from the subject matter in **WO'345** There is no similarity in WO'345 and IN'4412 as both WO'345 and IN'4412 relate to two separate inventions. Nowhere does the illustrative claims and specification of **WO'345** provide any information on the teaching of the present invention **IN '4412**.

Therefore the present invention is completely non-obvious over the cited prior art **WO2003059345.** The IN ‘4412 application provides the effects of both valsartan and sacubitril in a single compound . There is no reference whatsoever to a single dual-acting compound (unique novel compound) that combines two active ingredients by two different mode of action having an intricate network and stabilized by an involved network of ionic, hydrogen and coordination bonds, which has been described in various ways in the IN’4412 specification. Therefore, a person skilled in the art trying to achieve the objectives of the claimed invention will never consider the Document **WO2002006253** as relevant piece of art. In view of the above, the claimed invention is inventive over the Document **WO2002006253**. The Document **US5217996** is completely silent on any **dual-acting compound”, i.e. a single compound** that has two different modes of action disclosed therein . **US’996** discloses a sodium salt of sacubitril because the claimed compound is not a mere physical mixture of sodium salts of valsartan and sacubitril, it is a new and unique single compound.Therefore, the problem and solution focused by the Document **US5217996** and the instant Application is entirely different. Therefore. a person skilled in the art trying to achieve the objectives of the claimed invention will never consider the Document **US5217996** as a relevant piece of art. Thus, the claimed invention is therefore inventive over the Document **US5217996.** There is no teaching, suggestion or motivation in US’996 . WO ‘253 for a person skilled in the art to prepare a dual acting compound of the IN ‘4412 application (supramolecular compound) comprising Valsartan and Sacubitril. The problem and solution focused by the Document **EP0443983** and the instant Application is entirely different.Therefore IN 4412 is inventive over the cited document EP0443983. **Neither is there any teaching or suggestion** in **WO2004/078163** that to prepare a dual acting compound of the **IN ‘4412** application supramolecular compound comprising Valsartan and Sacubitril with features referred to in *paras 23-34* (about the invention) as well as elucidated in the patent specification. Therefore **IN 4412 is inventive over the cited document WO2004/078163** .

The claims of the cited prior arts WO 345; US’996 ,WO ‘253, EP 983 ,1538/CHENP/2004 , EP0498361 and CN1443176 etc. does not provide a clear guidance for the claimed dual-acting compound (unique novel compound) that combines two active ingredients with two different modes of action having an intricate network and stabilized by an involved network of ionic, hydrogen and coordination bonds. Opponents did not provide any reasons for selecting imaginary compound for inventive step analysis. Apart from, as discussed above there is no clear teachings in the prior art documents for a person skilled to arrive at a supramolecular compound (a single unique compound of the two said actives) as claimed by the Applicant that the invention according to **IN’4412** application relates to a **supramolecular compound** comprising two active ingredients/ moieties (a) an angiotensin receptor blocker (Valsartan), (b) neutral endopeptidase inhibitor (Sacubitril), Molecular formula of C288H330N36O48Na18•15H2O (M.W. 5748.03); The sodium cations are coordinated by oxygen ligands derived from **twelve carboxylate groups** and **eighteen carbonyl groups** (in the Sacubitril anions and Valsartan anions), and from 13 of the 15 water molecules (*page 29, 3rd para of the patent specification* of IN’4412 application). The interactions are defined in the specification wherein the sodium cations are preferably coordinated to several oxygen ligands which come from carbonyl and carboxylate groups (*page 11, para 3 of the complete specification*).
The teachings in prior arts WO 345; US’996 ,WO ‘253, EP 983 ,1538/CHENP/2004 do not either individually or in combination, render obvious to a person skilled in the art, the compound as claimed in the original set and the amended set of claims of the instant application. The question which must be asked is whether the person skilled in the art ‘would have’ investigated this possibility with the expectation of success and not whether they ‘could have’ which in the present case would not have as there is no motivation in the prior art to reach the present invention. Thus, D1- D4, neither individually nor in combination, suggest/ motivate a person skilled in the art to arrive at the claims as claimed in the original set and the amended set of claims of the instant application. the claimed invention is both structurally and functionally different from that of the Document **WO 345; US’996 ,WO ‘253, EP 983 ,1538/CHENP/2004** . Therefore. a person skilled in the art trying to achieve the objectives of the claimed

invention will never consider the Document D1 as a relevant piece of art. Thus, the claimed invention is therefore inventive over the Document **WO 345; US'996 ,WO '253, EP 983 ,1538/CHENP/2004 , EP0498361 and CN1443176** etc .

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Overall, none of the Documents **WO 345; US'996 ,WO '253, EP 983 ,1538/CHENP/2004 , EP0498361 and CN1443176 etc** provide any specific teaching or suggestion to develop .

Cocrystals are "solids" that are crystalline single-phase materials composed of two or more different molecular or ionic compounds generally in a stoichiometric ratio which are neither solvates nor simple salts. A person skilled in the art would require carrying out significant number of experiments to prepare the co-crystals / a supramolecular compound of the simple compounds and evaluation of biological activity in order to arrive at the claimed invention. In order to arrive at the present invention, a person skilled in the art has to first of all make the innumerable modification in the compounds taught in the cited documents, which is in no way obvious for a skilled artisan due to vast differences in the structures of the compounds disclosed in the Documents D1-D6 and that of the instant Application. Further, a person skilled in the art would have to form a co-crystal of compound of Formula (I) the claimed invention, which is again not obvious to a person skilled in the art, in light of the teachings of the cited Documents D1-D6, either taken alone or in combination. It thus follows that the claimed invention differs substantially from the cited Documents D1-D6. *It was **not a routine technique** to combine two active pharmaceutical ingredients ("APIs") into a single compound unpredictable art, therefore, slight changes in the structure can lead to different physiological and biological properties. Since the Documents D1-D3 and D4-D6 provide no suggestion for the claimed compounds, accordingly, the cited documents fail to render the pending claims obvious. Further, a person skilled in the art would have to form a co-crystal of compound of Formula (**Dual Acting Compound)**at the claimed invention, which is again not obvious to a person skilled in the art, in light of the teachings of the cited Documents D1-D6, either taken alone or in combination. It thus follows that the claimed invention differs substantially from the cited Documents D1-D6.*

None of the cited reference Almarsson et al , Morissette et. al , Aakeroy et al , Vishweshwar et al ,Etter et al., and Other Non-Patent Literature discussed during the hearing alone or in combination "teach", "suggest" or "motivate" the subject-matter as claimed in the present invention and it is non-obvious for a person skilled in the art to arrive at the present invention. So that the subject-matter as claimed in the present invention is inventive over the cited documents.

I find claimed invention inventive and non-obvious. Accordingly, the ground for lack of inventive step is rejected.

ANALYSIS ON SECTION 3(d)

The opponent 2 (Natco Pharma) submitted that the claimed compound is a new form of the pharmaceutical combinations comprising valsartan or pharmaceutically acceptable salts thereof and a neutral endopeptidase (NEP) inhibitor or a pharmaceutically effective salts thereof, taught in D1.

The opponent 2 (Natco Pharma) argued that D1 at page 2 discloses that *In one aspect the present invention relates to pharmaceutical combinations comprising valsartan or pharmaceutically acceptable salts thereof and a neutral endopeptidase (NEP) inhibitor or a pharmaceutically effective salts thereof, optionally in the presence of a pharmaceutically acceptable carrier and pharmaceutical compositions comprising them.*

The opponent 2 (Natco Pharma) argued *D1 discloses pharmaceutical compositions* ***VALSARTAN*** *or pharmaceutically acceptable salts thereof and* ***SACUBITRIL*** *or a pharmaceutically effective salts thereof, optionally in the presence of a pharmaceutically acceptable carrier and pharmaceutical compositions comprising them.*
The opponent 2 (Natco Pharma) submitted that VALSARTAN AND SACUBITRIL in combinations results indicate AN UNEXPECTED THERAPEUTIC EFFECT Of a combination according to the invention, achieves GREATER THERAPEUTIC EFFECT THAN THE ADMINISTRATION OF VALSARTAN, ACE INHIBITORS OR NEP INHIBITORS ALONE and promotes less angioedema than is seen with the administration of a vasopeptidase inhibitor alone , useful in the TREATMENT OR PREVENTION OF HEART FAILURE SUCH AS (ACUTE AND CHRONIC) CONGESTIVE HEART FAILURE, left ventricular dysfunction and hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation, atrial flutter or detrimental vascular remodeling.

The opponent 2 (Natco Pharma) further argued the claimed compound being a supramolecular complex of the combination taught in D1 squarely attracts Section 3(d).

The opponent 2 (Natco Pharma) argued that **Expert Affidavits** which incidentally are dated before the Form-13 dated June 6, 2020 under Section 57, the expert affidavits to demonstrate that the claimed compound is admittedly a co-crystal form of a known combination.

The opponent 2 (Natco Pharma) submitted that D4 (Morissette et al.) describes designing and preparing alternative crystalline forms like cocrystals where the convention crystal forms fails to have the desired effect. Similarly, **D5 (Almarsson et al.)** discusses the evolution of crystal engineering into a form of supramolecular synthesis and the problems and opportunities in the pharmaceutical industry.

The opponent 2 (Natco Pharma) argued that **Izzo et al**. fails to substantiate the contentions of the Applicant under Section 3(d). Izzo et al. concludes that crystalline valsartan/sacubitril 400 mg daily (1) is superior to valsartan 320 mg daily (i.e. valsartan separately) for lowering SBP – THAT THE COMBINATION WAS SUPERIOR TO VALSARTAN PER SE WAS KNOWN AT THE TIME OF THE INVENTION FROM THE DISCLOSURE OF D1.

The opponent 2 (Natco Pharma) refer to Figure 2 in **Izzo et al**. argued that Izzo et al. clearly states that LCZ696 has similar efficacy to the combination of free valsartan 320 mg plus free sacubitril 200 mg.
The opponent 2 (Natco Pharma argued that the claimed invention squarely attracts Section 3(d) and the Applicant has miserably failed to demonstrate any therapeutic efficacy as required under Section 3(d).

The opponent 4 (Dr. Reddy's Laboratories Ltd.) submitted that the compound Valsartan is known from the prior art D3 and sacubitril is known from D4. Further, the use of these compounds in combination as a treatment for heart failure is also already known from document D1 and disclosed before the filing of the present application. Additionally, D5 specifically discloses disodium salts of valsartan and D3 discloses sodium salt of sacubitril. The **complex** of the impugned application is a "mere new form" of valsartan as known in D3 and sacubitril as known in D4; also it is a "mere new form" of valsartan disodium as known in D5 and sacubitril sodium as known in D4; further it is a "mere new form" of a combination of valsartan and sacubitril.
The opponent 4 (Dr. Reddy's Laboratories Ltd.) submitted Izzo et al. (J Cardiovascular Pharmacology; Vol. 69 No. 6, June 2017; Annexure – B) to show that claimed co-crystal of sacubitril and valsartan have enhanced therapeutic over existing knowledge. Specifically, the applicant argued that LCZ696 (400mg) have 37% less percentage of valsartan over a combination of Valsartan (320 mg) and Sacubitril (200 mg) but have similar efficacy.

The opponent 4 (Dr. Reddy's Laboratories Ltd.) argued that LCZ696 400 mg have similar effectiveness for SBP control (57*% vs 56.7%*) as compared to a combination Sacubitril (100 mg) + Valsartan (320 mg), though it has almost 50% of Sacubitril as of LCZ696 400mg.

The opponent 4 (Dr. Reddy's Laboratories Ltd.) argued that the reading of **Izzo et. Al.** the analysis of the quantified data reveals that reduction in amount of Valsartan in LCZ696 led to concurrent reduction in the observed therapeutic effect as compared to physical mixture of Valsartan and Sacubitril and in fact, almost double dose of Sacubitril is required in LCZ696 to produce the same level of effect as that produced by physical mixture of Valsartan and Sacubitril.

The opponent no 3 & 6 (Kumar sushobhan &G. Srinivasa Rao) submitted that Valsartan with Sacubitril is a known substance with known efficacy, the claimed subject matter of impugned application attracts Section 3(d) and it is incumbent upon the Applicant to prove enhancement in therapeutic efficacy achieved by the complex which is the subject matter of impugned application as compared to the therapeutic efficacy of Valsartan with Sacubitril

The opponent no 3 & 6 (Kumar sushobhan &G. Srinivasa Rao) that Valsartan with Sacubitril is a known substance with known efficacy, the claimed subject matter of impugned application attracts Section 3(d) and it is incumbent upon the Applicant to prove enhancement in therapeutic efficacy achieved by the complex which is the subject matter of impugned application as compared to the therapeutic efficacy of Valsartan with Sacubitril

The opponent no 3 & 6 (Kumar sushobhan &G. Srinivasa Rao) argued that the evidence of Dr Motto- fails to demonstrate greater efficacy; it only states that the valsartan in Entresto is more bioavailable than marketed formulation of valsartan- there is no attempt to demonstrate any therapeutic efficacy;
Dr. Billa attempts no comparison of the therapeutic efficacy exhibited by LCZ696 with a therapy when Valsartan and Sacubitril administered together.

The opponent no 3 & 6 (Kumar sushobhan &G. Srinivasa Rao) argued that Izzo et al published in 2017: this paper states that the supramolecular compound/complex *has similar efficacy to the combination of free valsartan 320 mg + free sacubitril 200 mg.*

The opponent no 3 & 6 (Kumar sushobhan &G. Srinivasa Rao) argued that there is no direct comparison of composition of WO'345 with the supramolecular complex in the specification of IN4412. There is no data or any material to demonstrate the that therapeutic efficacy of the supramolecular complex greater than the composition of WO'345- rather it shows they have comparative effect at best. Thus, the Applicant has failed to demonstrate any therapeutic efficacy as required under Section 3(d).

The opponent 7 (Chirag Tanna) **submitted** that the affidavit of Dr. Motto (para 23), there is an attempt to show that the supramolecular complex has a faster dissolution rate as compared to the physical mixture of Valsartan and Sacubitril. None of this features in the application as filed – hence all of this cannot now be considered for purposes of section 3(d) assessment.

The opponent 7 (Chirag Tanna) **submitted** that the same dose of valsartan and sacubitril should have been administered in the study to all study participants in said study. Moreover there is no rationale provided in the article as to why the dose strength of **LCZ696 and valsartan that had been**

administered is not identical. In order to adjudge the enhanced therapeutic efficacy, it is important to administer an equal dosage of compounds being studied because an unequal amount of dosage will result in different plasma concentrations and levels of the compounds in the body and hence, it will be impossible to ascertain enhanced therapeutic efficacy. Due to the above, it is not possible to draw any meaningful conclusions regarding therapeutic efficacy from the study and the same should be disregarded

The opponent 8 (KETAKEE S. DURVE) **(KETAKEE S. DURVE**) **submitted** the complete specification fails in this respect because there isabsolutely no detail or explanation on how the complex results in enhancement in therapeutic efficacy, let alone a significant enhancement.

The opponent 8 (KETAKEE S. DURVE) **submitted** that said "Izzo et al." is to be considered, page 24, para 78 of the patent applicant's reply to the opposition shows that there is no "significant" difference in the efficacy between sacubitril+valsartan (D1A) versus sacubitril and valsartan in a complex (impugned application).

The opponent 8 (KETAKEE S. DURVE) **argued that** From D1A, combining valsartan and sacubitril in their salt forms was already known. Said D1A also expressly taught that administering them together as a combination resulted in enhancement of efficacy. At best, taking the most favourable position for the patent applicant, the present invention merely changes the mode of delivery, i.e., instead of using two chemical compounds in one physical carrier, the two chemical compounds are combined in a complex form. Ultimately, *in vivo*, the two active ingredients will separate from the complex and independently act to their respective modes of action. Thus, the present invention is merely a change in the mode of deployment of the active ingredients and nothing more. Such patents are certainly not intended to pass the threshold under section. 3(d).

The applicant submitted that the patent specification, the present invention is directed to a unique and novel dual-acting compound that has also been defined on *pages 9 and 10 of the patent specification as* **A compound having two actives with different mode of actions in one compound;** a chemical substance comprising covalent bonds within the two pharmaceutically active agents and non-covalent interactions (such as a hydrogen bonding, ionic bonds) between the two active agents.
The applicant submitted that the patent specification IN4412 discloses A "compound" in the present invention is intended to describe a chemical substance comprising covalent bonds within the two pharmaceutically active agents, the ARB and the NEPi molecular moieties, and noncovalent interactions between these two , Distinct from physical combination as described in WO 345. (*page 8 of the patent specification)*
The applicant argued that the purpose of the present invention, the applicant has defined "**supramolecular complex"** as an interaction between the two pharmaceutically active agents, cations and any other entity present by means of non-covalent intermolecular bonding between them *(page 10 last para of the patent specification).*

The applicant argued that **Dr. Myerson** also in paras 2.1 to 2.10 of his affidavit refers to the present invention as a "new / novel compound". **Dr. Motto** also in his affidavit at para 19 and 22, refers to the present invention a being "a single compound". *Feng et al* refer to LCZ696 as a potentially **promising novel active ingredient** in pharmaceutical products.

The applicant argued that the ground that the present invention is non-patentable under Section 25(1)(f) in view of Section 3(d) of the Indian Patents Act, the **Applicant disagrees** and **The applicant** submits that the claimed compounds of the IN '4412 application does not fall under the scope of Section 3(d) as it relates to a "**new/ novel and unique compound"** and section 3(d) does not apply to such a compound.

The applicant argued that the claimed compound is a unique and novel compound (or supramolecular complex), which comprises
a) **anionic** valsartan,
b) **anionic** sacubitril, and
c) **sodium cations** at a molar ratio of 1:1:3.
d) The compound may further contain water molecules, and has a hydration state defined in the claims by "x", which is 0-3 in claim 1, such as 0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 1, 2.25, 2.5, 2.75, or 3 (*p. 22 second to last paragraph and p. 23*).
e) The compound is stabilized by non-covalent interactions (including hydrogen bonds, ionic bonds and van der Waals forces).

The applicant further argued that the NOVEL compound claimed in claim 1 is a 'trisodium-Sacubitril-Valsartan' compound (and may also include water molecules) and is not a **new form** of **a** known substance nor is a salt of sacubitril or salt of Valsartan. The claims of the present invention is directed to a **new compound / a new dual acting compound** wherein the angiotensin receptor blocker (ARB) and neutral endopeptidase inhibitor (NEPI) are linked by non-covalent bonding having different modes of action present in **one compound.**

The applicant further argued the novel compound of the present invention is not a new form of the combination of Valsartan and Sacubitril disclosed in **WO 345** for the purpose of Section 3(d) of the Indian Patents Act. The present claimed **novel and unique compound** is not a physical mixture of individual Na salts of Valsartan and Sacubitril but a compound that exhibited distinctly different spectral features in comparison to 1:1 mixture of the sodium salt. *(page 46, para 3 of the patent specification*). The compound claimed in claim 1 is a 'trisodium-Sacubitril- Valsartan' complex (and may also include water molecules) and is not a new form of **a** known substance nor salt of sacubitril or salt of Valsartan.

The applicant further argued the present invention is not a polymorph (polymorph is of a single active)- **it is a new, single compound** per se, **having a completely new structure**. It is not a complex or combination or derivative in view of *Allergan vs Ajanta, IPAB.*

The applicant argued that the present invention is not a polymorph (polymorph is of a single active) or a salt of a known substance because the present invention **is directed to single compound per se, having a completely new structure wherein the interactions in the compound have been defined in the specification. The applicant submitted** that the said compound is not a polymorph of A known substance or a salt of a known substance (valsartan or sacubitril) Reference is made to the patent specification *at page 46 para 3 also referred to above in para 39 of the written submissions.*

The applicant argued that Co-crystals differ from polymorphs, which are defined as including 1) **singlecomponent crystalline** forms that have different arrangements or conformations of the molecules in the crystal lattice, 2) amorphous forms, and 3) multicomponent phases such as solvate and hydrate forms.5 Instead, co-crystals are more similar to solvates, in that both contain more than one component in the lattice. **The claimed compound of IN '4412 is neither a complex or combination for purposes of Section 3(d) in view of *Allergan vs Ajanta, IPAB.***

Applicants (Novartis AG) Arguments and Submission for efficacy

The applicant argued that **no 'known substance with known efficacy' known at the priority date for the purpose of Section 3(d). The novel supramolecular compound was not known at the**

priority date. The applicant argued that the compound is not a new form (for example a new polymorph or a new hydrate) of a previously known compound – it is a new, single compound per se, having a completely new structure.
The applicant argued As on the priority date of the present application for the purpose of Section 3(d): 1) Valsartan was a known substance with known efficacy. Valsartan has known efficacy by virtue of its approval as a marketable drug DIOVAN *(Annexure 2 of Dr. Myerson's affidavit)* in 1996 2) Sacubitril was a known substance but did not have any known efficacy.
The applicant submitted that Sacubitril efficacy for Section 3(d) was not disclosed in US5217996 nor was Sacubitril approved as a monotherapy drug. Sacubitril was approved as a drug only with the commercial product that came out of IN 4412, i.e. Entresto® is the first and only regulatory approval of Sacubitril. In other words, Sacubitril has not been approved till date as a monotherapy and was approved for the first time in Entresto®

The applicant further submitted that the **combination of sacubitril and valsartan as disclosed in WO 2003/059345 is not the known substance with known efficacy for Section 3(d) on at least two accounts**:
i. **That Section 3(d) requires "A" known substance and therefore a combination of sacubitril and valsartan (i.e 2 actives) cannot be "A" known substance under Section 3(d) or be considered a known substance in view of the IPAB order in *Ajanta vs Allergan*.**

The applicant argued that the 'trisodium sacubitril and valsartan complex' cannot be considered as the **same substance** of the "known substance" having "**known efficacy"** of either valsartan or sacubitril. It is for the first time **that two active ingredients** have been combined in a unique and novel and inventive compound having a specific structure and comprises anionic valsartan, anionic sacubitril, and sodium cations at a molar ratio of 1:1:3, optionally with water molecules.

The applicant submitted that Valsartan is the known substance with known efficacy for 3(d), the applicant relies on Izzo et al (*see abstract page 374 LHS*) confirms:
a) That 400 mg of trisodium compound of valsartan (206mg) and sacubitril (194 mg) mg
i. Is superior to valsartan 320 mg of Valsartan for lowering systolic blood pressure;
ii. has similar efficacy to the combination of free valsartan 320 mg + 200 mg;
iii. Represents optimal dosage for systolic hypertension and
iv. Is safe and well tolerated
b) Thus, similar efficacy is achieved with lower amount of valsartan in LCZ696 namely, 206 mg of valsartan from LCZ696 versus 320 mg of valsartan in the co-administered combination (ca. 37% less).
c) LCZ696 despite lower dosage of the actives, showed superior reductions from baseline in the mean sitting diastolic and systolic blood pressures compared to valsartan.
d) The author at page 380 LHS under the head "DISCUSSION" concludes that LCZ 400 mg is superior to monotherapy valsartan 320 mg of Valsartan for lowering systolic blood pressure (53.5 % vs 39.9 %).

Reduction in blood pressure

	SBP	DBP	PP
Valsartan (320mg)	**-9.6**	**-5.2**	**-4.4**

Sacubitril + Valsartan (400 +320 mg)	**-12.1**	**-5.8**	**-6.2**
LCZ696 (400mg)	**-13.0**	**-6.2**	**-6.8**

Reduction is SBP 53.5 % vs 39.9 %

The applicant submitted that **LCZ696** was tested in **1328 patients** and was **compared with valsartan** for reduction in blood pressure published by **Ruilope et al., 2010.**
Ruilope et al., 2010. Comparative date shown that

(a) with 200 mg sacubitril and 320mg valsartan, 400 mg LCZ696 (containing the equivalent amounts of 206 mg valsartan and 194 mg sacubitril) showed full additivity for reduction of mean sitting diastolic blood pressure, and more than full additivity for reduction of mean sitting systolic blood pressure underscoring the complementary effects of the dual mechanism of action.
b) From the compared dosages, namely 200 mg sacubitril and 320 mg valsartan which were compared with 400 mg LCZ696 (containing the equivalent amounts of 206 mg valsartan and 194 mg sacubitril); i.e., the amount of valsartan in LCZ696 is significantly lower (206 mg) than the amount needed when administered in the free acid form (320 mg).

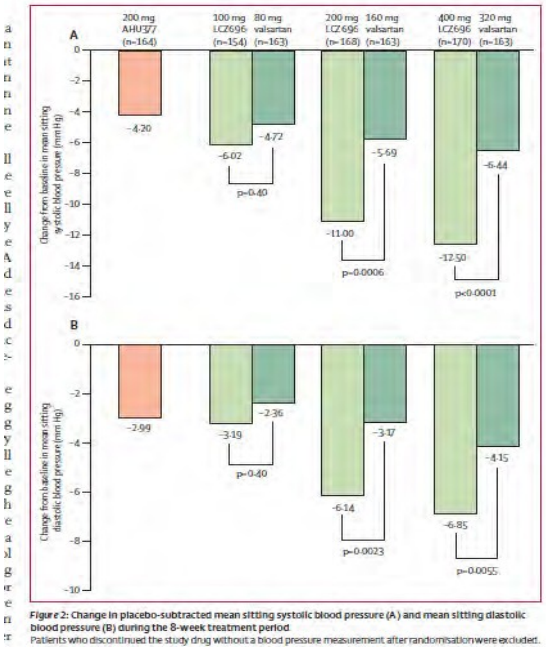

Figure 2: Change in placebo-subtracted mean sitting systolic blood pressure (A) and mean sitting diastolic blood pressure (B) during the 8-week treatment period
Patients who discontinued the study drug without a blood pressure measurement after randomisation were excluded.

The applicant argued that **LCZ696** show enhanced efficacy over Valsartan and improvement over the physical combination of Valsartan and Sacubitril.

Controller Coclusion on Section 3(d)

The claims of the present invention are directed to a **new compound / a new dual acting compound** wherein the angiotensin receptor blocker (ARB) and neutral endopeptidase inhibitor (NEPI) having different modes of action are linked by non-covalent bonding in **one compound.** Unite Sacubitril and Valsartan into a single chemical entity. The the claims of the present inventions are **novel and unique compound and which** is not a physical mixture of individual Na salts of Valsartan and Sacubitril but a compound that exhibited distinctly different spectral features in comparison to 1:1 mixture of the sodium salt. **The claim 1 of the present invention** is a 'trisodium-Sacubitril-Valsartan' compound (and may also include water molecules) and is **not** a **new form** of **a** known substance nor is merely a salt of Sacubitril or salt of Valsartan. **which is not a new form of a known substance nor is merely a salt of Sacubitril or salt of Valsartan in comparison with the cited prior documents cited by the opponents (1-8) .** The 'trisodium Sacubitril and Valsartan complex' cannot be considered as the **same substance** of the "known substance" having "known efficacy" of either Valsartan or Sacubitril. The claimed supramolecular compound is unique and is different from a physical mixture of Valsartan and Sacubitril , in that two active ingredients have been combined in a unique and novel and inventive compound having a specific structure and comprises anionic Valsartan, anionic Sacubitril, and sodium cations at a molar ratio of 1:1:3, optionally with water molecules. Patent specification has defined "supramolecular complex" as an interaction between the two pharmaceutically active agents, cations and any other entity present by means of non-covalent intermolecular bonding between them.

Controller coucluded that because of the following reasons and data, the efficacy shown in the present invetion is superior over the cited prior documents:

(1) Izzo article concludes that LCZ696 400 mg is superior to monotherapy Valsartan 320 mg for lowering systolic blood pressure (53.5 % vs 39.9 %) , despite lower dosage of the active Valsartan and similar dosage of the active Sacubitril, LCZ696 showed superior reductions from baseline in the mean sitting diastolic and systolic blood pressures compared to Valsartan alone. **The Izzo et al article clearly demonstrates that LCZ696 is far superior to the known drug Valsartan 320 mg and is well tolerated**.

(2) Dr. Gauri Billa's affidavit reported that LCZ696 after its approval is a **breakthrough product** and **class 1** recommendation for patient for HF with reduced ejection fraction (HFrEF), LCZ696 after its approval is a **breakthrough product** and **class 1** recommendation for patient for HF with reduced ejection fraction (HFrEF).

(3) The therapeutic effect of the claimed compound has been confirmed in the representative animal studies performed and described in the specification of the **IN '4412 Application** (***p. 33-35 and paras 2.1 to 2.11 of Dr. Myerson's affidavit)***.

(4) LCZ696 was tested in 1328 patients and was compared with Valsartan for reduction in blood pressure published by Ruilope et al., 2010.

(5) Ruilope authors, compared with 200 mg Sacubitril and 320mg Valsartan, 400 mg LCZ696 (containing the equivalent amounts of 206 mg Valsartan and 194 mg Sacubitril) showed full additivity for reduction of mean sitting diastolic blood pressure, and more than full additivity for reduction of mean sitting systolic blood pressure underscoring the complementary effects of the dual mechanism of action.

The compound LCZ696 of the present invention shown enhanced efficacy over Valsartan and

the physical combination of Valsartan and Sacubitril. Application clearly shows the efficacy of the 'trisodium Sacubitril and Valsartan complex' over cited prior arts documents cited. I am satisfied that claimed compound have enhanced efficacy. Therefore, the Pre Grant opposition with respect to Section 3(d) is not valid. . Accordingly, the ground for Section 3(d) is rejected.

I conclude that such a ground of opposition is not validly established by the opponents.

Analysis, reasons and decision on Insufficient disclosure

The opponent 2 (Natco Pharma) states that the complete specification of the alleged invention does not sufficiently and clearly describe the claimed invention. The Opponent states that it is a well settled rule that the specification should clearly and fairly describe the invention and disclose the best mode of working the invention so that the person skilled in the art could perform the invention without any undue efforts and it is hereby stated that the Applicant has failed to do so. The claims are unduly broad and claimed compounds of valsartan and sacubitril may have 0 to 3 degrees of hydration. Even though the applicant has claimed several hydrate forms in the claims, the specification only describes the preparation of only the hemipentahydrate form.

The opponent 2 (Natco Pharma) submitted that the applicant has claimed a range of molecular forms such as a hydrate, hemihydrate, monohydrate, sesquihydrate, dehydrate and trihydrate. Claim 1 on record encompasses several forms of the dual-acting compound, but the impugned specification does not sufficiently disclose the method of preparation ofall those compounds and the reaction conditions whereby all of the compounds of claim 1 may be prepared, except that for hemipentahydrate form. In absence of such preparation methods a person of average skill has to conduct undue experimentation in order to formulate such crystalline and salt forms. There is no example or description which would enable preparation of a supramolecular complex when x is = 0 i.e. the anhydrate form (without water). Examples 1 to 3 of the impugned application relate to the hemipentahydrate form, that is a compound where x is = 2.5.

The opponent 2 (Natco Pharma) argued that the Applicant is clearly trying to re-claim the combination in a surreptitious manner by making misleading statements since according to its own statement, in absence of water the HIGHLY INTRICATE SUPRAMOLECULAR STRUCTURE will not form.

The opponent 4 (Dr. Reddy's Laboratories Ltd.) submitted that the Applicant has failed to describe and disclose sufficiently in the complete specification. The best methods of developing the preferred embodiments of the compounds as claimed in claims 1 -5; The compounds comprising valsartan and sacubitril having 1 – 3 moles of sodium and 0 -3 moles of water; The synthesis of the complex as claimed in Claim 6 -8 is too vague and will not teach a person skilled in the art to arrive at the claimed supramolecular structure ; No clarity as regard to how the water molecules are associated to the compounds valsartan and sacubitril. The choice of alkali being Na+ finds no disclosure in the complete specification; The best dosage compositions of the preferred compounds inasmuch as the Patentee have provided only a generic composition of the effective drug containing any compound in claims 1-5. o The

Patentee has further failed to provide any ratios of the compound and excipients, failed to provide the effective dosage form and composition;

The opponent 4 (Dr. Reddy's Laboratories Ltd.) argued that the Patentee has also failed to provide the best methods of use of the said compounds. Further, the administration forms mentioned in the description are vague and too wide to include all possible routes of administration.

The opponent 4 (Dr. Reddy's Laboratories Ltd.) argued that Post Filing of the data showing efficacy of the application not admissible.

The opponent no 3 & 6 (Kumar sushobhan &G. Srinivasa Rao) submitted that the claims on record are very broad and claim compounds of valsartan and sacubitril wherein the ratio of the water in the complex is 0 to 3. There is no example or any guidance in the specification as to how a supramolecular complex can be formed when x is = 0 i.e. where water is not present. Similarly, there is no example to demonstrate as to how complex a complex can be formed when x is any value between 0 to 3 except 2.5. All examples pertain to a compound where x is = 2.5. This is important and relevant since the Applicant's own employee, PeterKarpinski has stated on oath that he had to conduct more than thousand experiments to arrive at the supramolecular complex where x is = 2.5. If the Applicant themselves have to conduct thousand experiments to arrive at a compound where x is = 2.5, it is but natural that arriving at a compound where x is any value from 0 to 3 except 2.5 would also involve equal number of experiments or undue experimentation .

The opponent no 3 & 6 (Kumar sushobhan &G. Srinivasa Rao) argued that the claims are not properly supported by the specification .

The opponent 7 (Chirag Tanna) **argued** that Claims are drawn to embodiments that are either not possible to achieve or are inoperable - Hence the claims are insufficient and invalid
The opponent 7 (Chirag Tanna) **argued** the claims include supramolecular complex of Sacubitril and Valsartan without the use of any solvent at all i.e. where x = 0 or in other words x is anhydrous. The claims also cover alternatives where x = 0.25 or 0.75 and other alternatives between 0 (anhydrous) and 1 However, there is no guidance in the specification or an example whereby any information can be gathered as to how to prepare a supramolecular crystal without the use of water- it is not even clear whether such a complex can be prepared at all- given that as per the Applicant themselves (Affidavit of Dr Motto para 5, 8, 10, 15 and Dr Karpinsky para 4), thousands of experiments and large number of resources/personnel/time were required to be carried out to arrive at a complex with 2.5 molecules of water.

The opponent 7 (Chirag Tanna) **argued that** If such huge amount of effort was required to generate complex with 2.5 molecules of water, equal amount if not less, would be required in order to arrive at complex with 0 (anhydrous form), 0.25 or 0.75 molecules of water.

The opponent 7 (Chirag Tanna) **argued that** Dr Karpinsky testifies that "undue experimentation" was required to arrive at a complex with 2.5 molecules of water. This fortifies the argument of the Opponent that arriving at a complex whether having 0 (i.e. anhydrous form), 0.25, 0.75, 1, 2 or 3 molecules of water requires undue experimentation and is a "mini-research program" i.e a new invention;

The opponent 7 (Chirag Tanna) **argued that** the Applicant themselves admit that a complex having 0 (i.e. anhydrous form), 0.25, 0.75, 1, 2 or 3 molecules of water requires huge amount of experimentation, then as per the settled law, the claims should be deemed to be not enabled by the specification and hence rejected on this ground alone.

The opponent 7 (Chirag Tanna) **argued that** Claim 6 : Step (i) of claim 6 reads as under: "dissolving (S)-N-valeryl-N-{[2'-(1H-tetrazole-5-yl)-biphenyl-4- yl]-methyl}-valine or a salt thereof and (2R,4S)-5-biphenyl-4- yl-4-(3-carboxy-propionylamino)-2- methylpentanoic acid ethyl ester or a salt thereof in a suitable solvent"

The opponent 7 (Chirag Tanna) **argued that** the specification (Page 35) lists out some solvents- such as "Solvents included in the scope of the present invention include, but are not limited to, solvents in which the ARB, NEPi and inorganic salt forming agent preferably exhibit a lower solubility that allows the linked pro-drug to crystallize. Such solvents may comprise, but are not limited to, water, methanol, ethanol, 2-propanol, ethylacetate, methyl-1- butylether acetonitrile, toluene, and methylene chloride and mixtures of such solvents" **The said claim 6 is thus not fully supported by the specification as all the solvents in the text book of chemistry are neither illustrated nor enabled by the specification. The entire range of the claim is not enabled.**
The opponent 7 (Chirag Tanna) **argued that** there is no guidance or a working example as to how one can obtain a crystalline supramolecular complex of Sacubitril and Valsartan without the use of any solvent at all i.e. where x = 0 (anhydrous form) or to obtain supramolecular complex with 0.25 or 0.75 water molecules. The specification or the examples do not specify anything about a supramolecular complex with 0 (anhydrous form), 0.25, 0.75, 1, 2 or 1.5 or 3 molecules of water or even.

The opponent 7 (Chirag Tanna) **argued that** several salt forming agents were attemptedthese include "....zinc hydroxide, calcium methoxide, magnesium hydroxide, sodium methoxide, sodium hydroxide, potassium hydroxide, lithium hydroxide….". However, , Dr Motto clearly and categorically states that "none of the experiments lead to crystalline material or generated solids". It is notable that the specification at page 35 describes and lists out various salt forming agents and included within this is, sodium hydroxide and sodium methoxide, which as per Dr. Motto do not work;

The applicant submitted that the Applicant has not only disclosed the invention but has also disclosed the most preferred embodiment of the said invention in the patent specification including its method for preparation. It is therefore submitted for "over disclosure" of the invention and disclosing the best embodiment and best mode of operation, the Applicant cannot be penalized.
The applicant submitted that the patent specification of **IN'4412** application clearly meets all the four corners of the said provision. Section 10(4) states as follows:
"*Every complete specification shall-*
(a) fully and particularly describe the invention and its operation or use and the method by which it is to be performed;
(b) disclose the best method of performing the invention which is known to the applicant and for which he is entitled to claim protection; and
(c) end with a claim or claims defining the scope of the invention for which protection is claimed;
(d) be accompanied by an abstract to provide technical information on the invention.

The applicant submitted the Applicant has in an unambiguous manner made a very clear disclosure in the patent specification. The content of aforesaid section in *paras 21 to 25* are not repeated for the sake of brevity.Under the head of "field of invention", the Applicant has stated that the present invention is

directed to ***dual-acting compounds*** and combinations of angiotensin receptor blockers and neutral endopeptidase inhibitors, in particular, a dual acting compound wherein the angiotensin receptor blocker and neutral endopeptidase inhibitor are linked via non-covalent bonding.Under the head 'Detailed description', the Applicant clearly provides the invention as being a dual acting compound wherein two active compounds with different mechanism of action namely an angiotensin receptor antagonist and a neutral endopeptidase inhibitor can form a unique supramolecular entity for the treatment of patients with various cardiovascular and/or renal diseases. **The applicant argued** tha**t** the patent specification clearly provides that the new supramolecular entity has distinct properties different to the physical combination as defined on page 9 of the patent specification of IN'4412 application. The supramolecular compound has also been defined as an "interaction" between the two actives to form a single compound.

The applicant argued that the Applicant has extensively disclosed the process of preparing the novel compound according to the present invention. *Reference in this regard is made to pages 37-41 of the specification of IN'4412 application.*
a) The specification further provides that the preferred molar ratio of Valsartan: Sacubitril in the compound is 1:1.
b) Further, with regard to the sodium cation, the specification further provides on page 22 that the preferred molar ratio in which Valsartan, Sacubitril and sodium cation is present is 1:1:3.
c) Therefore, the stoichiometric ratio of **Valsartan to Sacubitril to Sodium** in the preferred compound and also commercial product of the Applicant derived pursuant to IN'4412 is in the ratio of 1:1:3 that is specifically claimed by claims 1 to 3.
d) The hydration state of the said novel compound is also within a **narrow range** of 0-3 such as 0, 0.25, 0.5, 0.75, 1.25, 1.5, 1.75, 2.25, 2.5, 2.75, 3, preferably 2.5.

The applicant submitted that the dual acting compound of the present invention is characterized by very distinct spectral peaks and shifts that are not observed in the physical mixture. The preferred embodiment, '*tri-sodium-[3-((1S,3R)-1-biphenyl-4-ylmethyl-3-ethoxycarbonyl-1-butylcarbamoyl)-propionate-(S)-3'-methyl-2'-(pentanoyl{2''-(tetrazol-5- ylate)biphenyl-4'-ylmethyl}-amino)butyrate]-hemipentahydrate*' is exemplified in Examples 1-3 of the IN'4412 Application (*p. 40-43*) and is fully characterized by various analytical and spectroscopic techniques (*p. 24-29 and 43-45 of the specification*). The single crystal X-ray diffraction (SCXRD) data for the exemplified embodiment of the claimed supramolecular compound reveal a highly unusual and intricate threedimensional structure, as summarized on *page 28* of the specification of the IN'4412 Application.

The Applicant submitted that the preferred embodiment "hemipentahydrate wherein "x" is 2.5' *(see p. 22, second to last paragraph of the specification of the IN'4412 application)* has been exemplified in Examples 1-3.

The Applicant further submitted that Further, the compound in which x = 0.5 (hemihydrate) is disclosed in Example 3 of the specification. In example *3 at page 43 and page 46 of the patent specification of IN'4412 application*, the Applicant clearly states as follows:
"*As shown by DSC and thermogravimetric analysis (TGA), upon heating, the water of hydration is released in two steps: the first step occurs below 100°C and the second step above 120°C. Both DSC and TGA instruments are operated at a heating rate of 10 K/min*."
The Applicant submitted that Example 3 (*reference is made to Dr. Myerson affidavit para 2.10*) describes that a person skilled in the art would be able to vary the hydration level. The differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) showed that upon heating the water of hydration is released gradually from the exemplified hemipentahydrate compound in two steps: the

first step occurs below 100°C and the second step above 120°C. The loss of water in two steps in DSC/TGA studies – one step below 100°C and the second step above 120°C – is characteristic of a compound with multiple hydration states. During the first dehydration step, 80% of the water of hydration is lost (equivalent to two water molecules), yielding a hemihydrate compound (i.e. x = 0.5).

The Applicant submitted that the specification provides general methods which can be used to provide compounds of the invention. These methods are not limited to the formation of crystalline forms. For example, page 37, line 18 to page 40, line 24 of the specification describe in detail methods of preparing a dual-acting compound such as that of claim 1 by: (i) dissolving an angiotensin receptor antagonist (in this case valsartan) and a neutral NEPi (in this case sacubitril) in a suitable solvent, (ii) dissolving a basic compound of Cat (in this case sodium) in a suitable solvent, (iii) combining the solutions of steps (i) and (ii), (iv) precipitating the solid and drying the same to obtain the dual-acting compound (of claim 1) or obtaining the dual-acting compound (of claim 1) by solvent exchange. At no point is the method described as being limited to the formation of a crystalline form of the claimed compound.

The Applicant submitted that the support to solvent specifically acetone can be found in specification (see page no. 38 of IN'4412 application).

The Applicant argued that the specification provides general methods which can be used to provide compounds of the invention. These methods are not limited to the formation of crystalline forms. ***For example, page 37, line 18 to page 40, line 24 of the specification*** describe in detail methods of preparing a dual-acting compound such as that of claim 1 by: (i) dissolving an angiotensin receptor antagonist (in this case Valsartan) and a neutral NEPi (in this case Sacubitril) in a suitable solvent, (ii) dissolving a basic compound of Cat (in this case sodium) in a suitable solvent, (iii) combining the solutions of steps (i) and (ii), (iv) precipitating the solid and drying the same to obtain the dual-acting compound (of claim1) or obtaining the dual-acting compound (of claim 1) by solvent exchange. At no point is the method described as being limited to the formation of a crystalline form of the claimed compound. Additionally, the amorphous compound is obtained as an intermediate in Example 1 of the Patent. **In Example 1, a 1:1:3 molar ratio of Valsartan, Sacubitril and sodium hydroxide are dissolved, combined and stirred. T**he solution is evaporated to yield a glassy solid. The glassy solid is an amorphous form of the claimed compound. While this glassy solid is an intermediate, not a final product, in Example 1, that does not cast doubt on a single compound being obtained. A scientist could stop the experiment reported in Example 1 after the glassy solid was obtained and thus obtain the glassy solid as the final Product.

The Applicant argued that Dr. Karpinski's (inventor) affidavit was submitted before USPTO during the prosecution of US patent no. 8,877,938 in response to the objection of obviousness raised by the USPTO. It is pertinent to note that the USPTO raised the objection of inventive step and Dr. Karpinski's affidavit deals with the objection of obviousness and not insufficiency. In this regard, the Applicant draws attention towards the notice of allowance of US8,877,938 patent, enclosed as ***Annexure- 13***. As evident from above, Dr Piotr H. Karpinski affidavit filed before USPTO was in relation to 'Obviousness' and not 'Insufficiency'. The USPTO in the 'notice of allowance' clearly highlighted that over 1000 experiments were required to prepare the claimed crystalline compound, which demonstrates **undue technical hurdles and provides evidence of unpredictability** in achieving the claimed invention.
The Applicant argued that **the argument of the Opponent in relation to Dr. Karpinski affidavit is completely flawed.**

The Applicant futher submitted that Dr. Motto in his affidavit in particular para 3 has clearly identified the invention upon which the inventors of IN'4412 embarked an ***experimental quest***. The research carried out by the inventors of IN'4412 as stated in para 3 was to unite Sacubitril and Valsartan into a single

chemical entity. Further**,** *Dr. Michael Motto in para 3 of his affidavit* documented various strategies adopted by the inventors of **IN'4412** application and their failure**.**

The applicant argued that in relation to sufficiency, the scope of claim 1 is commensurate to the technical contribution provided in the specification of the IN'4412 application. The IN'4412 application relates to a new compound, which is claimed as different hydrates. Although, the IN'4412 application does not exemplify each and every hydrate within the scope of the claims, there is no requirement for the claims to be limited to the particular physicochemical form(s) that have been specifically exemplified in the description (*case law, FDC Ltd vs Sanjeev Khandelwal; and Tata Global vs HUL*). On the contrary, it is well established that disclosure of one way of making a new compound is sufficient to justify a claim that covers the compound and its derived forms in any physical form in which they may be obtained. This is because once a skilled person is given a new compound, variants such as polymorphs and hydrates would be considered routine to make using common general knowledge.

The applicant argued that Dr Dandala has relied on the definition of pharmaceutical co-crystal from the US FDA guidance document. the Opponent once again has not even understood what the invention is about.

Controller Conclusion on Insufficient disclosure

After listening to the arguments of the opponents and the applicant, it is observed the present invention is directed to ***dual-acting compounds*** and combinations of angiotensin receptor blockers and neutral endopeptidase inhibitors, in particular, a dual acting compound wherein the angiotensin receptor blocker and neutral endopeptidase inhibitor are linked via non-covalent bonding. The patent specification of **IN'4412** application to demonstrate that all the disclosures that is required under Section 10(4) of the Indian Patents Act is clearly contained therein. The Applicant has not only disclosed the invention but has also disclosed the most preferred embodiment of the said invention in the patent specification including its method for preparation. The Applicant clearly provides the invention as being a dual acting compound wherein two active compounds with different mechanism of action namely an angiotensin receptor antagonist and a neutral endopeptidase inhibitor can form a unique supramolecular entity for the treatment of patients with various cardiovascular and/or renal diseases. The patent specification clearly provides that the new supramolecular entity has distinct properties different to the physical combination as defined on page 9 of the patent specification of IN'4412 application. The supramolecular compound has also been defined as an "interaction" between the two actives to form a single compound. The Applicant has extensively disclosed the process of preparing the novel compound according to the present invention. *Reference in this regard is made to pages 37-41 of the specification of IN'4412 application.*The preferred embodiment "hemipentahydrate wherein "x" is 2.5' *(see p. 22, second to last paragraph of the specification of the IN'4412 application)* has been exemplified in Examples 1-3. The compound in which x = 0.5 (hemihydrate) is disclosed in Example 3 of the specification. In example *3 at page 43 and page 46 of the patent specification of IN'4412 application*. Dr. Motto in his affidavit in particular para 3 has clearly identified the invention upon which the inventors of IN'4412 embarked an ***experimental quest***. The research carried out by the inventors of IN'4412 as stated in para 3 was to unite Sacubitril and Valsartan into a single chemical entity.

After going through the arguments & submissions of both the all parties on the above mentioned ground where section 10(4) is in question, I find that the invention including the claimed compounds are sufficiently described and enabled in the patent specification. I note that Applicant has provided examples, schemes of synthesis, experimental data, figures, simplified structure , therapeutic efficacy data **(***The therapeutic effect of the claimed compound has been confirmed in the representative animal studies performed and described in the specification of the IN '4412 Application (p. 33-35 and paras 2.1 to 2.11 of Dr. Myerson's affidavit**)**.* and, sum formulas,Preferred solvents. A

person skilled in art will able to perform the invention in view of the description of the patent application. I am of the opinion that the complete specification of the patent application sufficiently and clearly describes the invention as well as the method by which it is to be performed.I found that invention claimed in claims is sufficiently and clearly described in the description, the complete specification. Hence I dismiss ground of opposition relating to section 25(1)(g) of notice of opposition. ***I conclude that such a ground of opposition is not validly established by the opponents.***

Section 8

The applicant submitted that the Applicant has complied with the requirement of Section 8.

a) Provided details of the corresponding application **20 times** on the following occasions. 17/12/2013; 23/05/2014; 16/06/2014; 12/01/2015; 29/05/2015; 18/11/2015; 07/12/2015; 28/04/2016; 01/11/2016; 28/02/2017; 10/04/2017; 01/11/2017; 28/03/2018; 20/09/2018; 22/03/2019; 24/10/2019, 02/04/2020; 08/09/2020; 08/03/2021; 10/05/2021; 11/05/2022 and 01/11/2022

b) Provided the information regarding search and examination report on multiple occasions along with allowed claims for the major countries. **26/05/2015; 27/07/2015; 4/08/2015; 07/12/2015; 28/02/2017; 10/05/2021**

The applicant argued that the applicant has dutifully complied with all requirements under section 8(1) and 8(2). It is submitted the Applicant has discharged its duty and obligation under Section 8 of the Patents Act. Further, the application is still in the examination stage and the Applicant will provide any information as and when requested by the Learned Controller under Section 8(2).

Analysis,reasons and decision (section 8) : Applicant had filed Form-3 on 17/12/2013; 23/05/2014; 16/06/2014; 12/01/2015; 29/05/2015; 18/11/2015; 07/12/2015; 28/04/2016; 01/11/2016; 28/02/2017; 10/04/2017; 01/11/2017; 28/03/2018; 20/09/2018; 22/03/2019; 24/10/2019, 02/04/2020; 08/09/2020; 08/03/2021; 10/05/2021; 11/05/2022 and 01/11/2022 with details of corresponding foreign applications. All the facts submitted by the agent and 137 petitions were considered. When these petitions are not allowed then it will cause loss to applicant. Therefore said petitions under Rule 137 are allowed and therefore irregularity in filing above Form-3 after prescribed period is corrected without detriment to interests of applicant. Hence I dismiss this ground of opposition regarding section 25(1)(h).

I conclude that such a ground of opposition is not validly established by the opponents.

FURTHER PRE-GRANT OPPOSSTION No.'s 9 &10

A series of pre-grant representations have been filed for the Patent Application No. **4412/DELNP/2007 (IN'4412).** From which a Video conferencing hearing held in between 12-19th May 2020 for total number of **1-6** Pre Grant Oppositions . In 2020, the applicant filed affidavits for which some of the opponents demanded cross examination.

12 July, 2022 order no W.P.(C)-IPD 91/2021 & CM 28/2022, CM 33-34/2021 **Honorable Delhi High Court** in order to expedite the decision on the application and the pre-grant opposition, the following directions are issued:

i) The Opponent is permitted to file affidavits of its own experts in rebuttal to the three expert affidavits filed by the Applicant, within a period of four weeks

ii) If any documents are filed by the Opponent along with the said expert affidavits, the same shall be dealt with by the Applicant by way of additional written submissions within one week thereafter, without any further documents being filed by the Applicant.

iii) The Opponent is also permitted to file its additional written submissions within two weeks after filing of additional written submissions by the Applicant. The written submissions filed by both the parties shall be considered by the Controller for final decision in the pre-grant opposition;

iv) Parties shall appear before the Patent Office on **5th September, 2022 at 2:30 p.m**. Both the Applicant and the Opponent shall be given one hour each to make their submissions.

v) The situation as it exists today is that there has been no ruling on any of the amendments which have been filed by the Applicant. Thus, before the commencement of oral hearing in the pre-grant opposition, the Controller shall communicate orally to both the parties as to which of the amendments are being allowed and which would be the final set of claims which is being considered for grant.

vi) On the said date, after hearing the parties for one hour each, the final decision on the application/pre-grant opposition shall be given by the **Patent Office on or before 15th November, 2022**. The final decision rendered shall be communicated to all the parties and shall also be uploaded on the website of the Patent Office;

A Hearing was held on **5th September 2022** as per the direction of the Honorable DELHI Court, In the meantime, another **Pre Grant Opposition no 7** has been filed. **Pre Grant Opposition no 7** has also heard on **7 September 2022**. In the meanwhile, on 2nd September 2022, another **Pre Grant Opposition No.8** was filed. As per the direction of the **Honorable Delhi high court**, the disposal of this application **IN 4412** was fixed by **15 November 2022**. **Nevertheless, the Controller fixed the hearing of Opposition No. 8 on November 3, 2022, giving primacy to Natural Justice and completed the hearing.** Even after that, immediately after completing the hearing by the Controller, another Pre Grant Opposition was filed. Thus two more Pre grant oppositions were filed on **3rd November 2022 and 4th November 2022** . Since as per the direction of the court it was necessary to dispose of this application by **15 November 2022**. Also, the controller carefully studied the grounds of Pre- Grant Opposition No. 9 and 10. But on studying the grounds of the Pre Grant Opposition Nos. 9 and 10, the Controller observed that **there is no separate merit in them**. All these grounds have already been heard in Pre grant oppositions No. 1 to 8. The Controller also observed that Even after completing the hearing of eight oppositions, these oppositions was only a delay tactic to prevent the disposal of the application from being completed by **15 November 2022.**

And there is no separate merit in all these oppositions. All of the prior art Cited in these have already been heard.

Table 1 : Comparative Mapping of Prior art cited by the Opponents

Prior Arts Cited	Indian Pharmaceutical Alliance& Mr. Hiren Darji	Natco Pharma	Dr. Reddy Laboratories	Mr. Kumar Sushobhan& Mr. G. Srinivasa Rao	Dr. Charanjit K. Sehgal	Dr. Ketakee Durve	Mrs Hemavathi. R	Dr. Kanchan Kohli
	Form 7A filed on 26-May-2016 & 25-Feb-2020	Form 7A filed on 6 Sep 2016	Form 7A filed on 14-Jun-2019	Form 7A filed on 25-Aug-2017& 18-Sep-2020	Form 7A filed on 20-May-2022	Form 7A filed on 02-Sep-2022	Form 7A filed on 03 November 2022	Form 7A filed on04 November 2022
WO2003/059345	D2	D1	D1	YES	YES	X	D2	D1
US5217996	X	D2	D4	YES	X	X	D5	D5
WO2002006253	D2/D5	D3	D5	YES	X	D1A	D6	D2
EP0443983	X	X	D3	X	X	X	D4	D4
WO2004/078163	D7	X	X	X	X	X	X	D3
CN1443176	X	X	X	X	X	D4	X	X
1538/CHENP/2004 / IN229051	D3	X	X	X	X	D1	D1	X
EP0498361A2	X	X	X	X	X	D2	D7	X
Morissette et. al.,	D6	D4	X	X	X	X	X	X
Aakeroy et. al.,	X		X	X	X	X	X	D6
Almarsson et. al.,	X	D5	X	X	X	X	X	X
Vishweshwar et. al.,	X	D6		X	X	X	X	X
Packer et. al.,	X	X	X	X	X		X	X
Etter et. al.,	X	X	D2	X	X	X	X	X

Table 2: Comparative Grounds of Opposition

Name of the Opponents	Prior Claiming	Novelty	Inventive Step / Obviousness	Sec. 3(d)	Insufficiency	Sec. 8
Indian Pharmaceutical Alliance	**YES**	**YES**	**Yes**	**YES**	**YES**	**YES**
Natco Pharma	NO	NO	**YES**	**YES**	**YES**	**YES**
Mr. Kumar Sushobhan	NO	**YES**	**YES**	**YES**	**YES**	**YES**
Dr. Reddy Laboratories	NO	NO	**YES**	**YES**	**YES**	NO
Mr. Hiren Darji	**YES**	**YES**	**Yes**	**YES**	**YES**	**YES**
Mr. G. Srinivasa Rao	NO	NO	**Yes**	**YES**	**YES**	**YES**
Dr. Charanjit K. Sehgal	NO	NO	NO	**YES**	**YES**	NO
Dr. Ketakee Durve	**YES**	NO	**YES**	**YES**	NO	YES
Mrs Hemavathi. R	**YES**	NO	**YES**	**YES**	**YES**	NO
Dr. Kanchan Kohli	NO	NO	**YES**	**YES**	**YES**	NO

In the recent case **Dhaval Diyora vs Union of lndia** , **WRIT PETITION (L) N0.3718 OF 2020** wherein the Hon'ble Bombay High Court held -

27. Further after the Controller rejects the patent application, the Appellate Board allows the appeal and directs the Controller to issue the patent, the matter proceeds beyond the first part of section 43, and the patent stands granted. By virtue of Section 117-D (2) the Controller is duty-bound to make necessary entries and seal the patent. **After the order of the Appellate Board, this only ministerial act remains. If after the order of the Appellate Board, which is to be implemented by the Controller, the Controller entertains pre-grant applications, it may give rise to an endless series of oppositions**. **This would mean, after the order of the Appellate Board but before the patent is sealed, one more pre-grant opposition can be filed seeking fresh hearing. If that is entertained and the patent is rejected and the appeal is allowed, again, one more pre-grant application can be filed. Such interpretation will do violence to the scheme of the Act.** Therefore the contention that the order passed by the Appellate Board was at the most finding that the patent was in order and it did not grant the patent, is not correct. The Controller rightly refused to entertain the Petitioner pre-grant opposition.

IPAB order No: OA/1/2021/PT/DEL following direction issued by the Hon'ble IPAB held:

1. **In order to overcome the undue delay in disposals of pre-grant oppositions, resulting from serial filing of pre-grant oppositions, the court directed that, if the Controller has heard all the existing parties in accordance with the teachings of Rule 55(5) and has reserved the order, he shall go ahead with pronouncement of such order, even if some pre-grant opposition is filed between the date on which he has reserved the order and the date of pronouncement of the order.**
2. **For the subsequent pre-grant opposition, the Controller shall make the opinion as to what substantial evidence, apart from those produced in the previous case is being produced which makes the second/subsequent pre-grant opposition maintainable. The e-module shall be suitably modified to that effect.**
3. **The Controller as per Rule 55 (3) consider the pre-grant representation in each and every case and if he opines that the patent application shall be refused or requires amendment, then before giving notice to the applicant of patent, he should make such opinion annotated in the patent application file, even if such file in maintained electronically. The e-module should be updated to that effect.**

Controller observation , conclusion and analysis for pre grant opposition (filed by Mrs Hemavathi. R) and (filed by Dr. Kanchan Kohli) :

The Pre Grant Opposition **(Mrs Hemavathi. R**) and opposition (**Dr. Kanchan Kohli**) **is dismissed** due the following reasons :

(1) After observation of the **table 1** and **table 2** ,It is cocluded that there is no **separate merit** in all these oppositions. All of the grounds and prior arts Cited in these oppositions have already been heard in the hearing of the previous pre grant oppositions **1-8.**

(2) As per the direction of the **Honorable Delhi high court**, the disposal of this application **IN 4412** was fixed by **15 November 2022.**

(3) These oppositions was only a delay tactic to prevent the disposal of the application from being completed by **15 November 2022.**

(4) that there is no **AID OF EXAMINATION** in all these oppositions.

(5) **After completing hearng of the 8 oppositions and direction issued by the Delhi high court if the Controller entertains pre-grant applications, it may give rise to an endless series of oppositions .**

Analysis, reasons and decision:

Learned opponents Mrs Hemavathi. R and Dr. Kanchan Kohli has not filed any new ground under Section 25(1) and there is no **separate merit** in all these oppositions. All of the grounds and prior arts Cited in these oppositions have already been heard in the hearing of the previous pre grant oppositions **1-8.** There is no **AID OF EXAMINATION** in all these oppositions.

Hence I refuse notice of oppositions of opponents Mrs Hemavathi. R and Dr. Kanchan Kohli.

I dispose the interlucatory petition and petitions filed by the applicant taken on record on public interest. After consideration of the submissions made by both the parties and the amendments so far made by the applicant, in view of reasons in above paragraphs, as per Rule 55(6) of Patents Rules 2003 hereby reject the all pre-grant representation (1-10) order that the instant application shall proceed for the grant of patent.

Hearing under section 14

A Hearing under section 14 has been conduted on **02.12.2022, at 11.00 am** at Delhi patent office,

Objections :

(1) Use claims 4,5 can not be allowable under section 2(1)(j) of the Patent Act 1970 as amended in 2005.
(2) Title inconsistent with description and claims. Title should be in accordance of claim.
(3) Claim 4 fall under section 3(d) of the Patent Act 1970 as amended in 2005.

Applicant's written submissions:

TITLE

(a) In order to comply with the objection, the title of the invention has been revised to the ***'A Dual Acting Compound And Process For Preparing The Same'.*** The Applicant in this regard is enclosing revised form 1, 2 and abstract.
(b) Accordingly, the revised claims are attached as under:
a. claim 4 has been deleted; and
b. claim 5 has been revised l[as now claim 4).

Conclusion

In view of all above mentioned detailed discussion in the light of all the submissions of all opponents and applicant; and arguments before hearing by the applicant and all Opponents, the facts given in the documents submitted by all the parties, the all pre-grant representations are hereby I find claimed compounds are novel, inventive and patentable under Patents Act. Accordingly, the instant application as titled ***'A Dual Acting Compound And Process For Preparing The Same'.*** is allowed to proceed for grant with finally amended **claims 1-7** as filed by the applicant.

There is no order as to the costs.

Dated this 14th December, 2022

(Dr. Rajendra Kumar Lohiya)
Assistant Controller of Patents & Designs

Copy to:

(1) NOVARTIS AG.,

(2) Indian Pharmaceutical Alliance

(3) Natco Pharma Ltd.

(4) KUMAR SUSHOBHAN

(5) Dr. Reddy's Laboratories Ltd.

(6) Mr. Hiren Darji

(7) G. Srinivasa Rao

(8) CHIRAG TANNA INK IDEE,

(9) KETAKEE S. DURVE

(10) **Mrs Hemavathi. R**

(11) **Dr. Kanchan Kohli**