BEFORE THE CONTROLLER OF PATENT

PATENT OFFICE, DELHI

THE PATENTS ACT, 1970 (AS AMENDED)

SECTION 25(1)

In the matter of

Patent Application Number 2891/DELNP/2013 AND

In the matter of a

Pre-grant opposition to the grant of a patent thereon under section 25(1)

Enanta Pharmaceuticals Inc., USA. - The Applicant

The Delhi Network of Positive People (DNP+) & Initiative for Medicines, Access & Knowledge Inc. (I-MAK) - The Opponent

Present in hearing held on 06/09/2022 under section 25(1)

Ms. Archana Shanker, Ms. Vidisha Garg - For the Applicant

Dr. Muthu Venkatesh Sudali

Mr. Eashan Ghosh, Mr. Vineesh Kedaram . - For the Opponent

Ms. Tanya Verma

DECISION

1. An application for patent with application number 2891/DELNP/2013 was filed on 02/04/2013 by the Applicant for the alleged invention entitled "Macrocyclic proline derived HCV serine protease inhibitors".

2. The request for examination regarding this application was filed on 10/10/2013. This application was examined in accordance with the provisions of sections 12 and 13 of the Patents Act 1970 (as amended) and First Examination Report (hereinafter will be mentioned as FER) was issued to the Applicant's Agent on 30/05/2018. The FER contained both technical and formal objections. The Applicant's Agent filed a response to the FER on

27/08/2018 with their observations regarding the objections raised in FER along with amended claims.

PRE-GRANT [SECTION 25(1)] PROCEEDINGS

3. A representation under section 25(1) of the Patent Act was filed on 12/06/2019 against the instant patent application by the Delhi Network of Positive People (DNP+) & Initiative for Medicines, Access & Knowledge, Inc. (I-MAK).

The grounds of opposition under section 25(1) were as follows:

i. *Sec. 25 (1) (e): Obviousness and lack of inventive step;*
ii. *Sec. 25 (1) (f): Not an invention within the meaning of the Patents Act- (u/s 3d)*
iii. *Sec. 25 (1) (g): The complete specification does not sufficiently and clearly describe the invention.*

A notice was issued by email to the Applicant's Agent, with a copy of said notice to the Opponent, on 26/08/2021 under rule 55(3) of the Patents Rules (as amended) with the detailed statement of the grounds of opposition and copy of the prior art documents cited by the Opponent. Applicant was intimated that, if they are interested in contesting said representation, they may file the reply statement and evidence within three (3) months from the date of the said notice. The agent for the applicant sought an extension of time to file reply statement and evidence under rule 6(6) in view of the Hon'ble Supreme Court Order dated September 23, 2021 and corresponding notification of the Patent Office dated October 3, 2021. The agent for the applicant also filed a petition u/r 137 read with Rule 128 to condone the delay in filing the reply statement and evidence. The applicant filed a reply statement under rule 55(4) of Patents Rules, 2006 on 31/12/2021. The said petitions are allowed and the reply statement and evidence filed by the applicant is taken on record. Subsequently a hearing letter was issued on 23/03/2022 to the applicant and the opponent informing them the date of hearing in respect of the above-mentioned representation under section 25(1) of the Act (pre-grant opposition) which was fixed on 16/06/2022. The said hearing was adjourned twice on the basis of requests for adjournment filed by the applicant on 10/06/2022 and 11/07/2022. Finally the hearing

was scheduled on 06/09/2022 at 11:00 AM through Video Conferencing in Patent Office and both the parties (Applicant & Opponent) were instructed to be present before the undersigned on said date & time.

4. The hearing under section 25(1) of the Patents Act was held on the stipulated date i.e. 06/09/2022 which was attended by both the applicant and the opponent. Both the parties were instructed to file the written note of arguments within a period of fifteen days from the date of hearing under rule 28(7) of The Patents Rules (as amended).

5. The following documents as filed by both the parties are considered-

a) Pre-grant opposition under section 25(1) of the Act as filed by the opponent on 12/06/2019 along with evidences;

b) Reply statement and evidence as filed by the applicant on 31/12/2021 in reply to pre-grant opposition;

c) Written hearing submission filed by the applicant on 20/10/2022;

d) Written hearing submission filed by the opponent on 21/09/2022.

Though all the documents and submissions filed during proceedings of pre-grant representation are considered while deciding upon the present case but for the sake of brevity all the submissions and arguments are not being repeated here to the fullest extent and only submission provided by both the parties after hearing is reproduced herein.

GROUNDS OF OPPOSITION:

6. Ground (I) : Section 25(1)(e) – *Obviousness/lack of inventive step*

6(a) Submission filed by the opponent:

A. Priority Date

(i) The impugned application claims priority from 3 earlier patent applications which are summarized below:

Priority	Application number	Priority date
1	US61/385,058	21 September 2010
2	US61/499,994	22 June 2011
3	US61/504,616	5 July 2011

(ii) The earliest claimed priority date for the impugned application is thus 21 September 2010. The impugned application was originally filed with 26 claims. The applicant reduced the claims to 10 in response to the First Examination Report (FER). Claim 1, and therefore related Claims 2-10, of

the amended set of claims were not disclosed in either the first or second priority applications.

(iii) What survives for adjudication before the Ld. Controller presently are two claims. These were abridged by the Applicant on 31 December 2021. The Opponent submits that the surviving lead Claim 1 was first claimed as Claim 6 of US '616. Accordingly, the earliest effective priority date for the current pending claims derive priority from US '616 from US 61/504,616 dated 5 July 2011. In the light of the above, any patent/ application filed prior to the impugned application ought to be treated as prior art for the purpose of the grounds raised in this opposition.

(iv) In response, the Applicant has claimed that the priority for the impugned application is claimed from all three priority documents above. The Applicant asserts that the surviving claims are "fairly based" on matter disclosed in all three applications, within the meaning of Section 11(3) of the Patents Act.

(v) However, on facts, the Applicant's own best case to claim priority from US '058 (21 September 2010) is that:

a. Compound 6 in US '058 corresponds to Example 6 in the impugned application; and

b. Formula 7 of Claim 7 in US '058 corresponds to Claims 1-2 in the impugned application.

(vi) The Opponent submits that, under Section 11(3), two eventualities are provided for. One is where the priority for the claim is fairly based on disclosures in one of two or more priority documents [Section 11(3)(a)]. The other is where the priority for the claim is fairly based on disclosures partly in one and partly in another of two or more priority documents [Section 11(3)(b)].

(vii) Set against this, even by the Applicant's own best case, therefore, there is no claim-to-claim mapping with US '058 (or indeed, US '994, 22 June 2011) as the sole priority document. The claims in the impugned application are, at most, fairly based in more than one priority document. Under Section 11(3), the rule on such facts is that the later of multiple priorities will be read against the impugned application (in this case, 5 July 2011, corresponding to US '058).

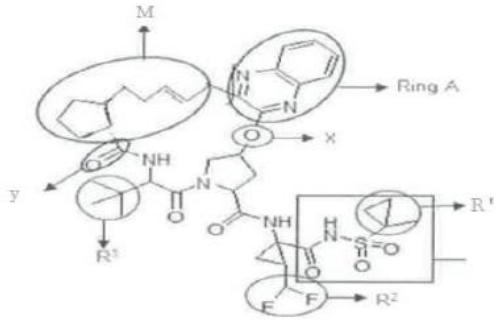
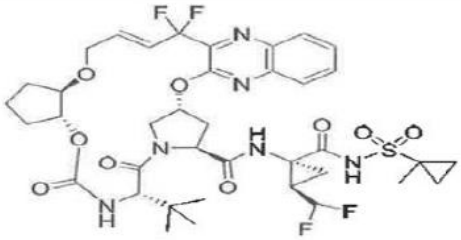
B. Lack of Inventive Step

(i) The Opponent submits that a strong case for lack of inventive step is made out in light of the prior arts disclosed in the Opposition.

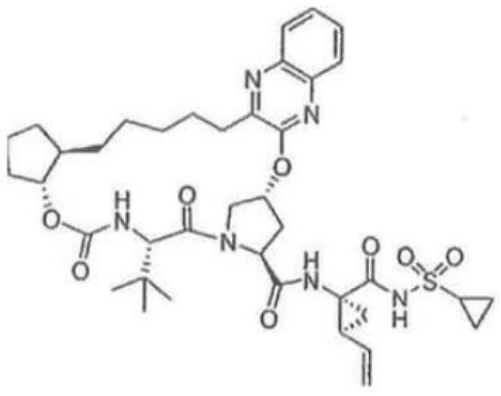
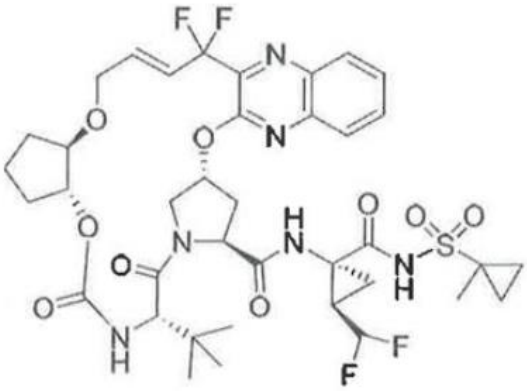
(ii) More specifically, the Opponent submits:

a. WO2008/057209 (May 2008) offers three iterations [Formula (I), Example 108, and Examples 120 and 134 collectively] that map directly onto certain core elements and functions of the impugned application. This is represented in the side-by-side comparisons below:

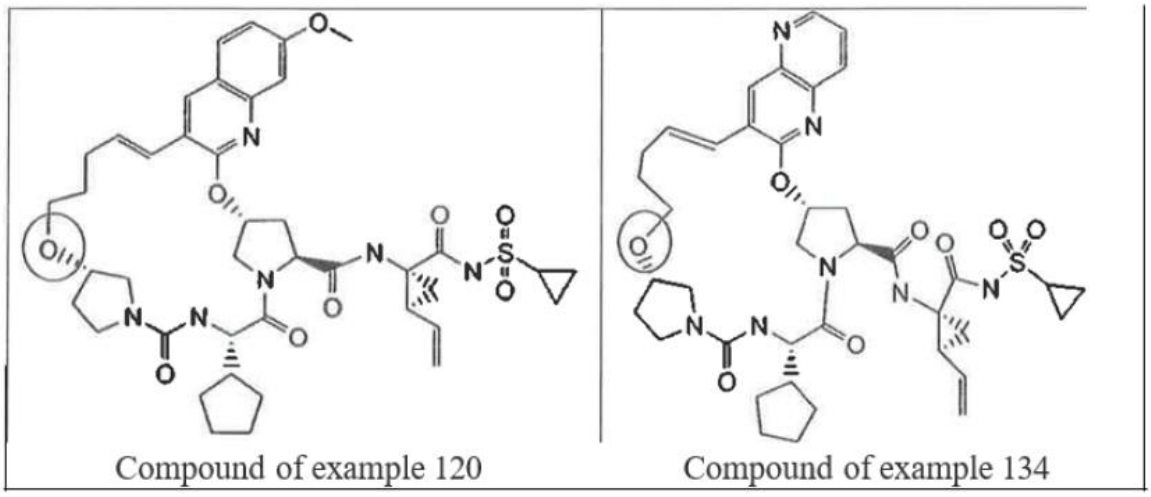
[Formula (I) of WO2008/057209 vs Claim 1 (Glecaprevir)]

	
Compound that can be deduced from the above highlighted substituents	Glecaprevir which is claim 10 of the impugned application

[Example 108 of WO2008/057209 (Annexure VI) vs Claim 1 (Glecaprevir)]

	
Compound of Example 108 (of Annexure VI)	Glecaprevir which is claim 10 of the impugned application

[Examples 120 & 134 of WO2008/057209]



Taken together, the above iterations insert into the prior art:

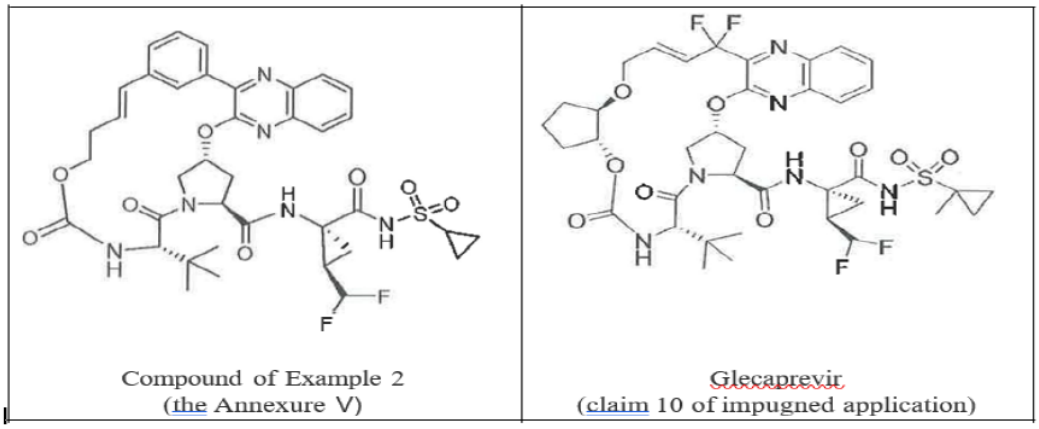
(1) Same central core as Glecaprevir (the subject of the impugned application), showing the same function and medical/therapeutic properties, with similar lateral chains;

(2) Same cyclopentyl ring as Glecaprevir and does not include an aryl ring linked to the quinoxaline group as in Glecaprevir

(3) Same – O – linkage between carbonyl group and cyclopentyl ring.

b. WO2009/064975 and WO2008/057209 or WO2009/108507 (May 2009) offers two iterations [Formula (XV) read with Example 2 and Formula (I), p. 4, read with Table I to III] that map directly onto certain core elements and functions of the impugned application. This is represented in the side-by-side comparison below:

[Formula (XV) read with Example 2 of WO2009/064975 vs Claim 1 (Glecaprevir), p. 16 of Opposition]



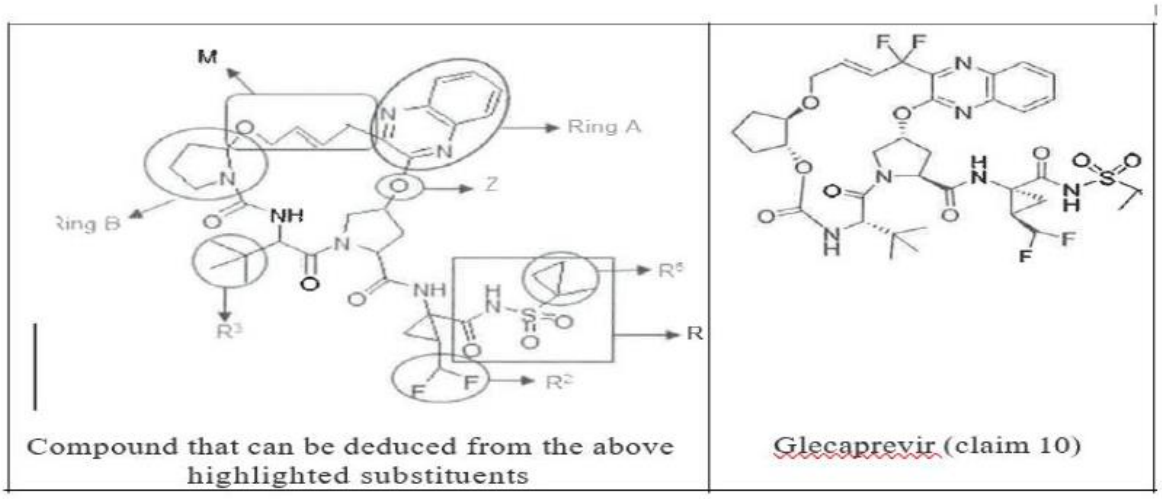
Taken together, the above iterations insert into the prior art:

(1) Same central core as Glecaprevir (the subject of the impugned application), showing the same function and medical/therapeutic properties, with similar lateral chains;

(2) The teaching that any person skilled in the art looking for an alternative anti-HCV compound to the disclosure in Example 2 of Annexure V would, after studying Annexure V, been able to provide a modified alkene chain with a di-fluoro substituent and add a methyl substituent on the terminal cyclopropyl ring, leaving only the differences of (i) absence of an aryl group linked to the quinoxaline group in Glecaprevir and (ii) presence of – O – linkage connecting a cyclopentyl ring with the alkene chain.

c. Similarly, WO2009/108507 (September 2009) provides another iteration [Formula (I)] that offers an alternate path to the – O – linkage connecting a cyclopentyl ring with the alkene chain (otherwise missing from Annexure V above). This is represented by the side-by-side comparison below:

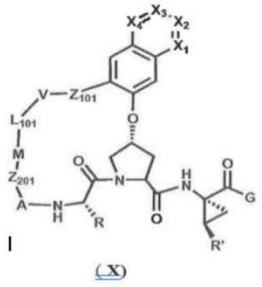
[Formula (I) of Annexure VII vs Claim 1 (Glecaprevir), p. 24 of Opposition]



3. With the above disclosures unequivocally forming part of prior art, the Opponent submits that WO2010/132163 (November 2010) (Annexure IV) offers a definitive iteration [Formula (X) read with Example 662 and p. 107, Line 3] that renders the impugned application completely obvious. This prior art, WO '163 (Annexure IV), is another application of the present Applicant itself. It qualifies as prior art for the present purposes on account of the priority date for the impugned application being 5 July 2011, as already detailed above.

4. More specifically, Formula (X) read with Example 662 of Annexure IV provides:

[Formula (X) with Example 662 of Annexure IV]



From this comparison, it is evident that:

(1) Set against Glecaprevir, the only difference qua Example 662 to Formula (X) of Annexure IV is the presence of a quinoxaline group in Glecaprevir rather than a quinoline group.

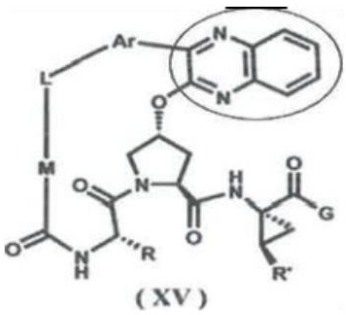
(2) This difference, too, is covered off by Page 107, Line 3 of Annexure IV, which lists a quinoxalinyl functional group as a possible substituent in this position.

(3) Accordingly, no technical advance can be claimed (and, certainly, none has been demonstrated by the Applicant) owing to the specific presence of the quinoxaline group in the impugned application.

(4) As such, the problem sought to be targeted by the impugned application could simply be formulated by providing further anti-HCV compounds of Example 662 of Annexure IV. The quinoxaline disclosure at Page 107, Line 3, would, in any event, prompt a person skilled in the art to try this substituent instead of the quinoline ring in Annexure IV.

(5) Annexure IV can further be read with Formula (XV) to Annexure V, represented below:

[Formula (XV) of Annexure V, with quinoxaline ring circled, p. 13]



Taken together with specific substitutions in Example 2 of Annexure V, it is clear that any person skilled in the art, seeking an alternative anti-HCV compound to Example 662 of Annexure IV above would have considered this compound from Annexure V. This is especially because quinoxaline and quinoline are both closely linked heterocyclic aromatic organic compounds having approximately the same molar mass, and because such substitutions with functionally close groups is common practice (para 7.2.2 of the Opposition).

6(b) Submission filed by the applicant-

As is evident from the pre-grant opposition, the ground of lack of inventive step is based on the following:

Lack of inventive step in view of documents

- WO '163 and WO '975 and
- WO '975 and WO '209 or WO '507

WO2010/132163 IS NOT A PRIOR ART

It is submitted that the case of the Opponents is based on the fact that Example 662 of WO '163 (Annex IV) discloses a compound similar to the pending claims of the present invention and therefore the compound of the present application lacks inventive step. This comparison is legally and technically flawed.

No argument either novelty or inventive step can be entertained based on WO '163 as the said document is not a prior art. WO' 163 was published after the earliest priority date, US 61/385058 (P1) dated September 21, 2010. WO '163 was published on November 18, 2010, which is after the priority date of the present application.

The claimed compound of the present invention is entitled to the following priority dates-

Priority Document	**Application Number**	**Priority Date**
1	US61/385,058	21-09-2010
2	US61/499,994	22-06-2011
3	US61/504,616	05-07-2011

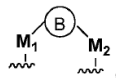
The Opponents have argued Annexures in the order, Annexures VI (WO '209) followed by VII (WO '507) and V (WO '975) and finally Annexure IV (WO

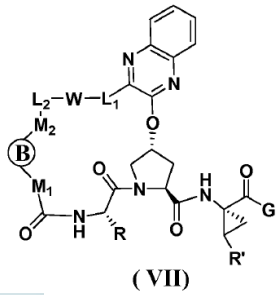
‘163). The choice of order is that the publication date of Annexure IV (WO ‘163) is November 18, 2010, which is later than the earliest priority date of the present application, which is P1-US61/385,058 - September 21, 2010.

The present pending claims is restricted to the compound i.e., Glecaprevir and its salts, which is disclosed as well as enabled in all the three priority documents.

Herein below we provide the reference of the claimed compound in all the three priority documents

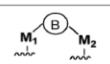
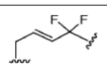
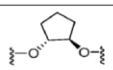
1) US61/385,058 - Table 1, Example 6, pages 10-11 (abridged) and 80

Representative compounds of the invention include, but are not limited to, the following compounds (example 1 to example 256 in Table 1) according to Formula VII wherein R, -L_2-W-L_1-,  , R’ and G are delineated for each example in Table 1.



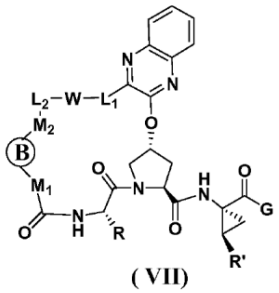
(VII)

TABLE 1

Example #	R	-L_2-W-L_1-		R’	G
6.					

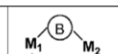
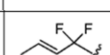
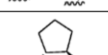
2) US61/499,994 - Table 1, Example 6, pages 13-14 (abridged) and 88

Representative compounds of the invention include, but are not limited to, the following compounds (example 1 to example 256 in Table 1) according to Formula VII wherein R, -L_2-W-L_1-,  , R’ and G are delineated for each example in Table 1.

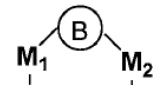


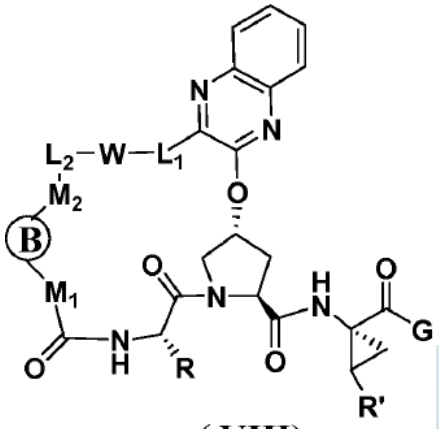
(VII)

TABLE 1

Example #	R	-L_2-W-L_1-		R’	G
6.					

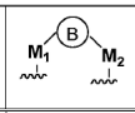
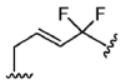
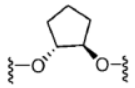
3) US61/504,616 - Table 1, Example 6, pages 14-15 (abridged), and 93

Representative compounds of the invention include, but are not limited to, the following compounds (example 1 to example 256 in Table 1) according to Formula VIII wherein R, -L_2-W-L_1-,  , R' and G are delineated for each example in Table 1.



(VIII)

TABLE 1

Example #	R	-L_2-W-L_1-		R'	G
6.					

It is respectfully submitted that under Section 11(3) of the Indian Patents Act, the claims of complete specification have to be fairly based on the matter disclosed in the priority application.

In this regard, reference is made to the following decisions:

- In the Matter of the Mond Nickel Company Ld.'s Application for a Patent. [1956.] REPORTS OF PATENT, DESIGN, AND TRADEMARK CASES [No.9] 189" Page 194, line 10-22: It seems to me that there is a three-fold investigation which is called for. Firstly, one has to enquire whether the alleged invention as claimed can be said to have been broadly described in the provisional specification, and only if an affirmative answer is given to that question does one proceed to the second question, which is: Is there anything in, the provisional specification which is inconsistent with the alleged invention as claimed? If it is found, upon examination, that the invention as characterised in the claim includes something which is inconsistent

with that which is described in the provisional specification, as at present advised I should think that it would be right to conclude that that claim could not have been fairly based upon the disclosure; but, assuming that those two burdens are satisfactorily surmounted, there is, I think, a third matter for enquiry; Does the claim include as a characteristic of the invention a feature as to which the provisional specification is wholly silent? It is with those approaches which I have indicated that I have to consider the submissions which have been made to me in the present case.

In the present case, the compound Glecaprevir is not only fairly based but there is an actual disclosure of the same in all the three priority documents and therefore is also entitled to the priority date of P-1 i.e 21st September 2010

In view of the above, any argument or representation in relation to WO '163 as being prior art for inventive step analysis has to be disregarded.

The Opponents have relied upon the following documents at the hearing for lack of inventive step:

Annexures	Document	Publication date	Comment
IV	WO2010132163A1	18-11-2010	Not a valid prior art, as it is published **after** earliest priority date (P1-US61/385,058 - **21st September 2010**)
V	WO2009064975A1	22-05-2009	
VI	WO2008057209A1	15-05-2008	
VII	WO2009108507A1	03-09-2009	

The Opponents in their written statement of opposition have taken two approaches for showing that the compound claimed in the present invention is obvious in view of Annexure IV to Annexure VII.

a. The first approach was to cherry-pick substituents from compounds/ Markush structure of Annexures IV and V and combine them to create a hypothetical structure that does not even resemble Glecaprevir.

b. The second approach was to combine the cherry-picked substituents from various structures of Annexure V, VI and VII.

However, as stated above, the Opponents during the hearing changed their approach of combining the documents. This is called HOP- SCOTCHING which is impermissible. Once a case is made out by the Opponent, they are not permitted to change their position. This is the law as laid down by Hon'ble Justice Prabha Sridevan in OA/17/2012/PT/KOL (order 162 of 2013) in Fresenius Kabi Oncology Limited vs Glaxo Group Limited (para 90) *"We doubt if such hip-hopping over prior arts would be possible unless the Hopscotchoutline of the Invention was before Ms. P. Sita. Too many randomly made right choices cannot be called a matter of obviousness".*

Further in the said order, in para 91, the IPAB clearly elucidates that the Opponent has to clearly provide as to why a choice for a particular prior art or a substituent is to be made without the knowledge of the claimed invention.

"The applicant does not tell us why the persons skilled in the art would select those examples in Exhibit-1 containing a Furan ring as the starting point at every stage. There were several options available in the generic structure shown in Exhibit-1 and only by a purposive choice, the invention compound can be arrived at. Similar is the case with Exhibit- 2. To show obviousness, it must be explained why the persons skilled in the art would choose from Exhibit-2 a furan ring substitution on the quinazoline ring out of the 39 examples. Many of the substituents on the quinazoline ring include only Methyl Sulphonyl, Nitro, Amino, Amino Methyl, Morphilino Ethyl etc., The applicant does not say why out of the separate individual possibilities these specific substitutions were made at the 4- position on the quinazoline , and the substitution at the 4'position of the phenyl ring of the aniline and also the 2-furyl ring substitution at the 6th position with the further substitution on the 5th position of the furan. The obviousness disqualification would arise only if the invention appears obvious from the teachings of the prior art. The choices that the applicant has made for R1, X1 , Q1, substituents and Q2 could have been made only if the person skilled in the art had the invention itself before her, otherwise each choice had to be made from multiplicity of choices for which they should be a logical explanation as to why these choices were made or these choices were apparent/obvious."

The Applicant will address all the documents as per the pleading in the written statement.

A. LEGAL PRINCIPLES OF OBVIOUSNESS

Section 2(1)(ja) defines inventive step to mean "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".

a) Obviousness is a mixed question of law and fact

Roche vs. Cipla, RFA (OS) 92/2012

- Para 111: Obviousness has to be strictly and objectively judged. In the decision reported as (1979) 2 SCC 511Bishwanath Prasad Vs. Hindustan Metal Industries (para 25) the Supreme Court laid down the principles to test inventive step'

- Para 118 : To determine obviousness / lack of inventive steps the following inquiries are required to be conducted

Step No.1 To identify an ordinary person skilled in the art,

Step No.2 To identify the inventive concept embodied in the patent,

Step No.3 To impute to a normal skilled but unimaginative ordinary person skilled in the art what was common general knowledge in the art at the priority date.

Step No.4 To identify the differences, if any, between the matter cited and the alleged invention and ascertain whether the differences are ordinary application of law or involve various different steps requiring multiple, theoretical and practical applications,

Step No.5 To decide whether those differences, viewed in the knowledge of alleged invention, constituted steps which would have been obvious to the ordinary person skilled in the art and rule out a hindsight approach. [PARA 118 of the order of the Division bench of Delhi High Court in Roche vs CIPLA, RFA 92/2012]

b) Structural similarity cannot form the basis of obviousness test

Division bench of Delhi High Court in Roche vs CIPLA, RFA 92/2012

Para 121 "Thus to show obviousness besides structural similarity there should be a reason or motivation shown in the prior art to make the

particular structural change in order to achieve the properties that the applicant was seeking."

- Mere structural similarity between a prior art compound and the claimed compound does not inform the lead compound selection. Otsuka Pharm. Co. v. Sandoz Inc., 678 F.3d 1280, 1292 (Fed.Cir. 2012); see Daichii Sankyo Co. v. Matrix Labs., Ltd., 619 F.3d 1346, 1354 (Fed.Cir. 2010). Proof of obviousness of a chemical compound "clearly depends on a preliminary finding that one of ordinary skill in the art would have selected [a particular prior art compound] as a lead compound." Takeda, 492 F.3d at 1357. The second step of the obviousness analysis requires a showing that the prior art would have taught a skilled artisan to make "specific molecular modifications" to a lead compound so that the claimed compound may be made with a reasonable expectation of success. Id. at 1356-57 (emphasis supplied).

Roche vs. Cipla, 2015, DHC (Single Bench)

- If the chemical compounds are held to be obvious on the basis of mere perusal and appearance of the structures and assuming that the slight change here and there is inconsequential without a positive evidence medically and clinically as to how the said reaction is immaterial, then several novel compounds can be declared obvious by such exercise and the same shall affect the research process adversely. The innovation or invention in the sense of chemical compound is not merely to innovate a new set of the compound per se but also making improvements in the existing state of the art by taking the aid of the already existing compound and working upon the same by way of experimentation by way of the reactants. This is the reason why, the Court cannot simply be satisfied by mere reliance of similar structure in the previous art and thereafter assuming that slight substitutions are inconsequential. Therefore, the establishment of the material facts is essential, which is missing in the present case.

Resultantly, no ground of obviousness or lack of inventive step under Section 64 (1) (f) of the Patents Act is made out due to the inability of the defendant to discharge the onus casted upon it.

c) The biological activity of a molecule has to be seen as a whole

[Merck vs Glenmark, order of Delhi High Court, para 105 and para 85]

Para 105 - "It is readily evident that the two molecules have very little in common when complete structures are compared. It is worth pointing out here that the biological activity of a molecule and its utility as a medicine is completely dependent on the structure as a whole. That is, each part of the molecule makes some contribution to the overall biological effect."

Para 85 - "Further having realized the missing parts in the hypothetical patch compound, the Defendant went hop-scotch searching"

d) The inventive step analysis has to be carried out by a person skilled in the art who is a hypothetical person who has the following characteristics

[Order of the Division Bench of Hon'ble Delhi High Court, in Roche vs CIPLA, 2015 in para 112]

a) that of a person who practices in the field of endeavour,

b) belongs to the same industry as the invention,

c) possesses average knowledge and ability and

d) is aware of what was common general knowledge at the relevant date.

e) POSA: Inventive step has to be decided through the eyes of a person skilled in the art and therefore the qualifications a POSA have to be defined

[Para 42 of the IPAB order in OA/8/2009/PT/CH, in Sankalp Rehabilitation Trust Vs. F. Hoffmann-La Roche AG] 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….."

f) A person skilled in the art reads the prior art as a whole and does not cherry-pick passages from a prior art

[Para 42 of the IPAB order in OA/8/2009/PT/CH, in Sankalp Rehabilitation Trust Vs. F. Hoffmann-La Roche AG] "POSA 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. … (Emphasis added)

g) Hindsight is impermissible to determine inventive step

[Para 113 of Merck vs Glenmark, order of Delhi High Court]

"None of the cited prior art documents lists the exact structural pieces that can be combined or attached to any of the core structures in order to arrive at Sitagliptin and the Defendant admits as much by stating that the fragments they have crafted in their arguments will have to be combined, as illustrated for example in paragraph 91 above. Yet the Defendant never tells us what will motivate the skilled person to carry out this combining of substituents and fragments. In fact, the only obvious motivation could be knowledge of the structure of Sitagliptin beforehand, which clearly derives only from hindsight."

h) Coherent Thread – There must be a coherent thread leading from the prior arts to the invention. Further, the tracing of the thread must be an act which follows obviously.

[Enercon (India) Limited vs Aloys Wobben, IPAB, ORA/08/2009/PT/CH, order 123 of 2013]

"The mere existence in the prior arts, of each of the elements in the invention, will not ipso facto mean obviousness. For after all most inventions are built with prior known puzzle-pieces. There must be a coherent thread leading from the prior arts to the invention, the tracing of the thread must be an act which follows obviously. We must apply this reasoning to test if indeed it is obvious, or if it seems to us to be obvious to the person skilled in the art because of what we know now. If it is the latter, it is hindsight deduction and is not acceptable, but if it is the former, then the patent must go."

i) For an obviousness, an element of directness must be there

[Para 11. 14.3.2 of FMC Corporation & Anr. v Best Crop Sciences LLP & Anr., CS(Comm) 69 of 2021, judgement dated July 07, 2021 by the Hon'ble Delhi High Court] Para 11. 14.3.2-

"In principle, I am inclined to agree with this test, to determine whether a patent discloses a particular invention or moiety which becomes, therefore, obvious from the patent. From the teachings in the genus patent, the person

skilled in the art must be in a position to arrive, without unduly straining his imaginative and creative faculties, at the specie patent, in order for the specie patent to be invalidated on the ground of obviousness. The element of "directness" must be there. The choice which the person skilled in the art would make, by way of substitutions on the Markush moiety or otherwise, must be apparent from the teachings in the genus patent, in order for the specie patent to be treated as "obvious". A "trial and error" approach would be antithetical to any suggestion of "obviousness".

j) Non-analogous art cannot be considered for obviousness analysis

[Pharmacyclics vs Laurus Lab, IPAB, OA/46/2020/PT/DEL]

16.18 For "inventive step" determination the prior arts should be analogous. In order for a reference to be proper for use in an obviousness rejection, the reference must be analogous art to the claimed invention16. We are of the firm opinion that the prior arts chosen by the opponents are not analogous and any determination of inventive step based upon the non-analogous prior arts is not going to yield proper result.

k) OTSUKA Case

The Court proposed a two - step analysis for determining obviousness of structurally similar compounds.

• The first step is to determine "Whether a chemist of ordinary skill would have selected the asserted prior art compounds as lead compounds or starting points for further development efforts" page 17

• The second step is to determine whether the prior art would have supplied one of ordinary skill in the art with a reason or motivation to modify a lead compound to make the claimed compound with a reasonable expectation of success" page 19

That absent a reason or motivation based on such prior art evidence, mere structural similarity between a prior art compound and the claimed compound does not inform the lead compound selection" page 19

l) Fresenius Kabi Oncology Limited vs Glaxo IPAB, 162/2013 para 90

"We doubt if such hip-hopping over prior arts would be possible unless the Hopscotchoutline of the Invention was before Ms. P. Sita. Too many randomly made right choices cannot be called a matter of obviousness".

m) Search and Examination Guidelines

Page 26: On the other hand, a generic disclosure does not impugn the novelty of a more specific claim, so that an earlier reference to a metal coil spring cannot be used to attack the novelty of a claim specifying such a spring made of copper. In some cases, however, the disclosure of a comparatively small and restricted field of possible alternatives.

n) The aforesaid principles can be summarized as follows:

a) Obviousness is a mixed question of fact and law and therefore has to be adjudicated by way of legal principles and material facts.

b) Obviousness has to be judged through the eyes of a person skilled in the art (POSA) and the qualities of POSA includes

i. POSA is a person who practices in the field of endeavour, belongs to the same industry as the invention, possesses average knowledge and ability and is aware of what was common general knowledge at the relevant date. POSA will not consider non-analogous art i.e. prior art that is not related to the patent /patent application in dispute.

ii. POSA is not an inventor or an expert;

iii. POSA is conservative and does not take risk;

iv. POSA reads prior art as a whole and learns from the teaching of a document as a whole; and

v. POSA neither picks out the teaching towards passages like the challenger nor is he seeking out teaching away passages like the defender.

c) Inventor knowledge or path adopted by the inventor is irrelevant in an obviousness enquiry.

d) To inquire into obviousness, two-fold inquiry is required to be conducted i.e. motivation to select and motivation to modify.

e) Mere structural similarity cannot form the basis for selection of a lead compound.

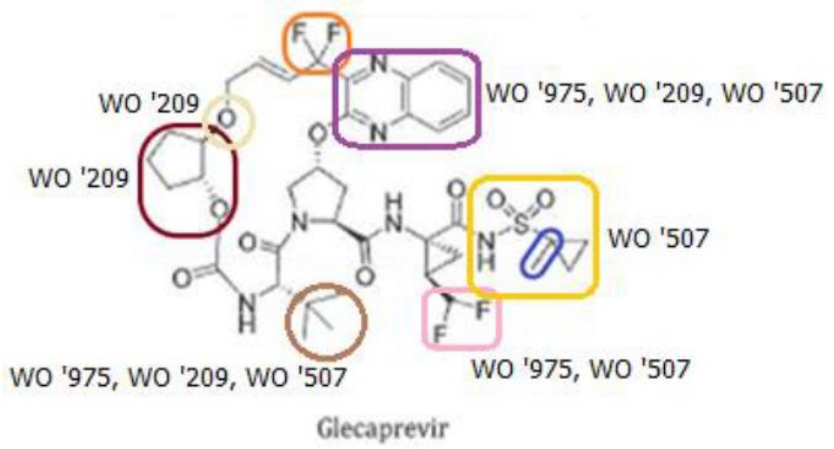
f) Cherry picking and hindsight are not permissible.

g) Hopscotch searching for documents to fill in the missing gaps is not allowed

h) All inventions are built with known prior art puzzle pieces but there has to be a coherent thread connecting them clearly derived from the documents.

i) Non-analogous art cannot be considered for obviousness analysis

CASE OF THE OPPONENT: The entire case of the Opponents on obviousness can be schematically represented as follows:



As can be seen above, after having knowledge of the compound (not permissible and known as hindsight and creating hypothetical structures, the Opponent could still not arrive at the claimed compound according to the present invention.

C. DOCUMENT ANALYSIS

The Applicant regarding the documents considered by the Opponent for obviousness analysis submits as follows:

CLAIMS ARE INVENTIVE OVER WO2010132163 – (Ann-IV)

WO2010132163 (Publ. date: Nov. 18, 2010) – is not a prior art for obviousness analysis, as it is published after the priority date.

The argument of Opponent is frivolous and legally flawed: Without prejudice to the above,

• this document is completely silent regarding biological activity of the compounds taught.

• No rationale/motivation for selecting example 662 for further modification and substituting the quinoline with quinoxaline ring. (Among 918 compounds disclosed in WO '163)

Mere strong structural resemblance does not determine the similar activity (HCV NS3 protease inhibitory activity). For establishing obviousness, one needs to show the motivation of selecting a lead compound from a prior art.

WO '163 is not a prior art and therefore no arguments either in the pleadings or written submission or made by the Opponent at the hearing can be considered.

The law is extremely clear. Any document that is published after the priority date of the patent application can neither be considered for novelty nor inventive step analysis.

Argument of Opponent is frivolous

➢WO '163 published after priority date

➢Silent regarding biological activity

➢No rationale/motivation for selecting example 662 for further modification and substituting the quinoline with quinoxaline ring. (Among 918 compounds disclosed in WO '163)

➢ Mere strong structural resemblance does not determine the similar activity (HCV NS3 protease inhibitory activity)

➢ Selection purely based on structural similarity without any motivation, hence Hind-sight approach after having knowledge of structure of compound of present application

CLAIMS ARE INVENTIVE OVER WO2009064975 – (Ann-V)

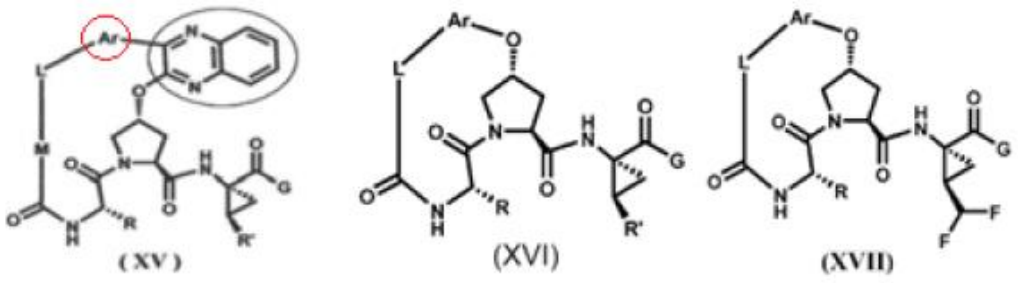
WO2009064975 (Ann-V) is related to macrocyclic compounds as HCV NS3 protease inhibitors (page 1, line 10-11) which contains quinoxaline ring

WO '975 discloses 1586 compounds of

a. Formula XV – Example 1 to 1506 in Table-1, page 17-129 (Not claimed)

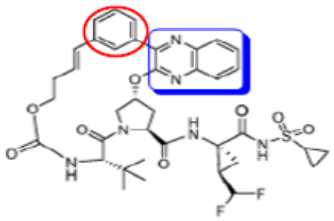
b. Formula XVI – Example 1507 to 1554 in Table-2, page 130-134 (Claimed)

c. Formula XVII – Example 1555 to 1586 in Table-3, page 134-137 (Claimed)



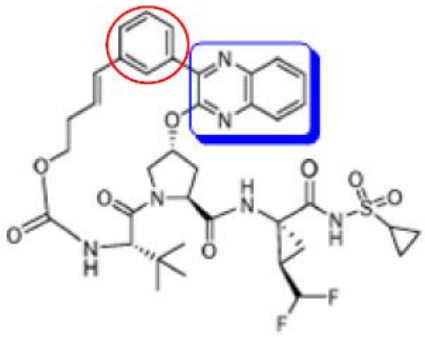
It is pertinent to mention that compounds of formula XV are not preferred compounds, as they are not even claimed.

The compounds of formula XV contain aromatic, heterocyclic or substituted aromatic ring attached to the quinoxaline ring at third position.
Example 2 of WO '975 is based on formula XV which is not even a claimed compound. The Opponent provides no logic or reasoning why Example 2 was selected from a not- preferred Markush structure

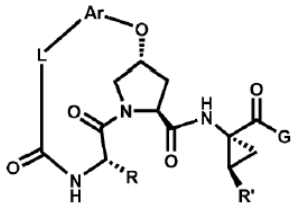


Example 2 of Annexure-V (WO '975)

Without prejudice, in example 2 compound contain phenyl ring on the 3rd position (RED) of the quinoxaline ring XV which is an integral part of the structure. There is no reason provided as to why would POSA be motivated to replace phenyl ring with di-fluoro substituents as envisaged in the present application.

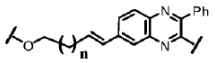
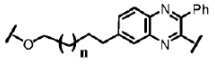
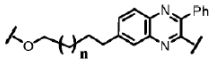
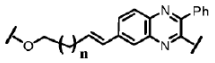
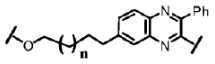


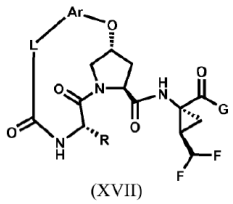
The claimed compounds claimed in Formula XVI and XVII – Example 1507 to 1554 of WO' 975 in Table-2, page 130-134 and Example 1555 to 1586 in Table-3, page 134-137 respectively discloses structurally completely different compounds, wherein the linker chain is attached to the aromatic ring and the phenyl on the heterocyclic ring in contrast to the teaching of the present invention.



(XVI)

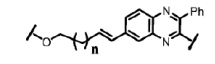
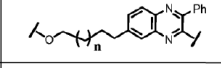
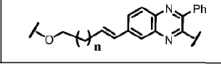
TABLE 2

Example #	R	L-Ar	n	R'	G
1507.			4		
1508.			4		
1509.			4		
1510.			3		
1511.			3		



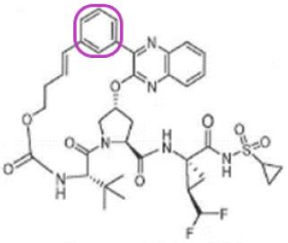
(XVII)

TABLE 3

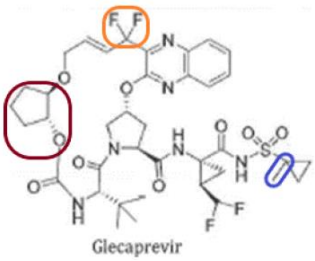
Example#	R	L-Ar	n	G
1555.			4	
1556.			4	
1557.			3	

The Opponents themselves have identified the structural difference between the claimed compound and prior art, WO '975. (*para 7.3 of Opposition Statement*)

The argument of Opponents is frivolous. Besides the several structural dissimilarities between the compounds of WO '975 the argument also has no merits for the following reasons:



Compound of Example 2



Glecaprevir

• WO '975 teaches structurally dissimilar compound

• Formula – XV which encompasses Example 2, is not claimed, in contrast Formula XVI and XVII is claimed which discloses structurally diverse compounds

• Absence of an aryl group linked to the quinoxaline group in glecaprevir;

• Presence of a -O-linkage connecting a cyclopentyl ring with the alkene chain in glecaprevir;

• Presence of a difluoro substituent on the alkene chain in glecaprevir;

• Presence of a methyl substituent on the terminal cyclopropyl ring in glecaprevir.

• None of the claimed compounds 1507-1586 contains di-fluoro on alkene chain or methyl substituent on the terminal cyclopropyl ring and also the cyclopentyl oxy as envisaged in glecaprevir

• Silent with regard to biological activity

• No element of directness (FMC Case)

• No teaching/suggestion to select (first step of Otsuka) and no motivation to modify (second step of Otsuka case)

• The selection of the document is merely for choosing the quinoxaline ring

• Provided no scientific rationale for selection of example 2 in WO '975

• In example 2, the quinoxaline ring is linked with phenyl ring at the third position and moreover the M-L linker is which is contrast to the teaching of the present invention.

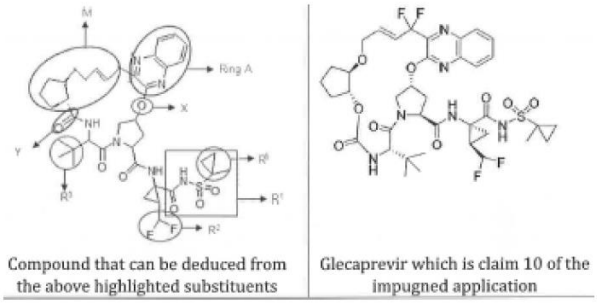
• As stated above including the case law, so many random choices without providing any reason is nothing but adopting a hindsight approach (see paras 90 and 91 of IPAB order 162/2013) referred to in para 32 of the submissions.

CLAIMS ARE INVENTIVE OVER WO2010132163 – (Ann-IV) and WO2009064975 – (Ann-V)

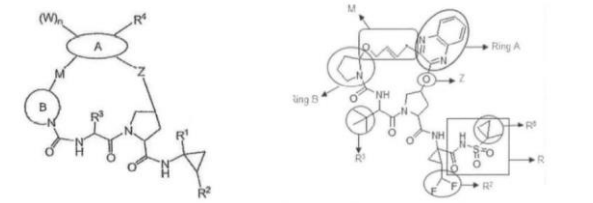
The Opponents arguments are legally incorrect as WO '163 is not a prior art and therefore cannot be combined with any other document.

OPPONENTS' ATTEMPT TO FILL IN GAPS OF TEACHINGS OF WO2009064975 WITH WO2008057209 AND/OR WO2009108507

The Opponent has further attempted to fill up the gaps of WO '975(Ann-V) and has relied upon the document(s) by combining the teachings with WO '209 or WO '507. The Opponent has attempted to deduce Glecaprevir from the substituents as illustrated below:

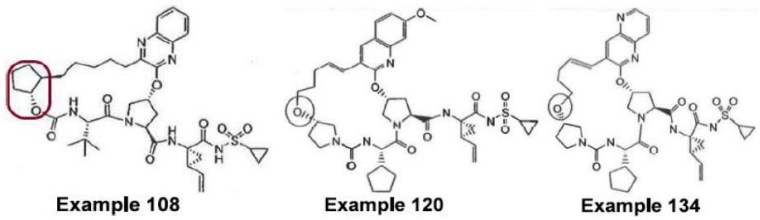


Compound that can be deduced from the above highlighted substituents | Glecaprevir which is claim 10 of the impugned application



Markush structure (I) | Compound deduced from the substituents disclosed WO '975 with WO '507

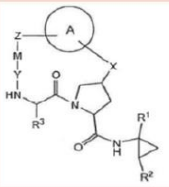
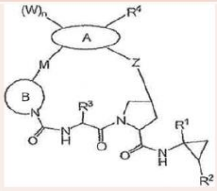
For this purpose, the Opponents have has referred to examples 108, 120 and 134 from WO '209 for filling the gaps of WO '975 to arrive at the structurally similar compound as glecaprevir.



Example 108 | Example 120 | Example 134

2. CLAIMS ARE INVENTIVE OVER WO2008057209 – (Ann-VI) and WO2009108507– (Ann-VII)

Both WO '209 and WO '507 are related to HCV NS3 protease inhibitors of Markush formula (I).

WO '209	WO '507
Markush Formula (I)	
	

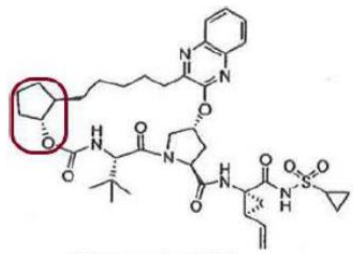
WO '209 document exemplifies 138 compounds with structurally diverse scaffold and differing the alkyl or alkylne chain length and is also silent with regard to its biological activity.

WO '507 discloses 45 compounds with structurally diverse scaffold altering the alkyl chain the B ring. In WO '507, none of the disclosed compounds is even remotely structurally similar. Hence Opponents deduced a hypothetical structure from the substituents of Markush for structural similarity.

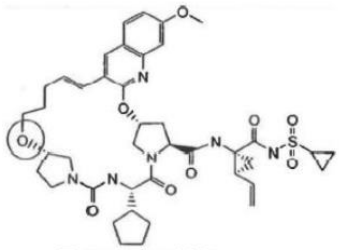
Teaching of the documents: Both WO '209 and WO '507 teaches to have alkylene group on the cyclopropyl ring and only the cyclopropyl ring without any substitution on the terminal end in contrast to the difluoro substituents and methyl substituent on the terminal cyclopropyl ring,

CLAIMS INVENTIVE OVER WO2009064975 – (Ann-V) and WO2008057209 – (Ann-VI)

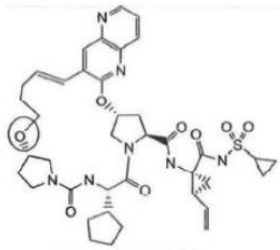
The Opponents have identified compounds in WO '209 for filling the gaps of WO '975



Example 108



Example 120



Example 134

a. The scaffold of Example 108 is quinoxaline. The cyclopentyl ring is linked at 3rd position through pentyl chain and differs in its basic scaffold and M-Chain.

b. The scaffold in example 120 is 7-methoxyquinoline,

c. The scaffold of example 134 is 1,5-napthyridine ring & M-chain is pyrrolidine ring linked through alkylene oxy chain (i.e., pentylene oxy chain).

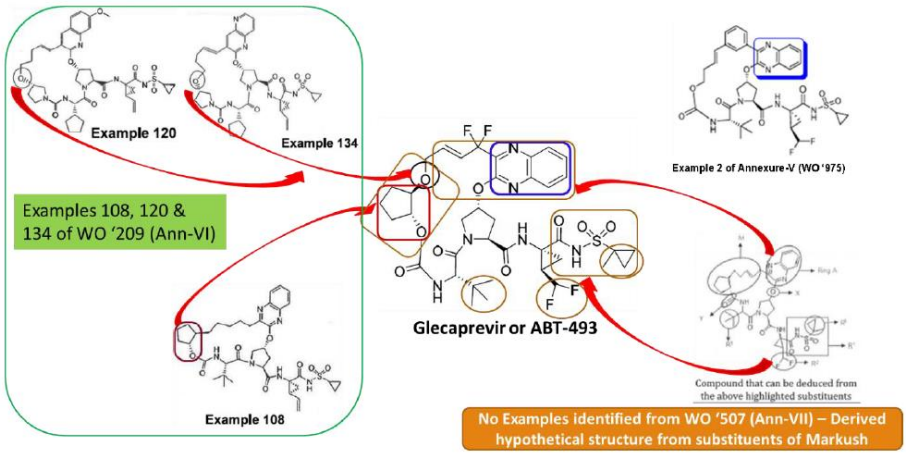
It is evident that the examples 108, 120 and 138 are structurally different from the above fact and the Opponent has provided no rationale/motivation

for combining the identified substituents of examples of WO '209 with example 2 of WO '975 and ignoring/ dropping the important features of the said compounds. In addition to several other changes, the Opponent ignored that Glecaprevir has 1,1-difluorobutyl- 2,3-ene-4-oxy chain. This selection of the compounds and choice of substituent are purely based on a hindsight approach. Even after this, the Opponents were still not able to arrive at Glecaprevir. It is well known to POSA, that the molecule as a whole is responsible for biological activity and any change (small or big) can alter biological activity to a great extent.

CLAIMS INVENTIVE OVER WO2009064975 – (Ann-V) and WO2009108507– (Ann-VII)

WO '507 has been referred in European Supplementary Search Report under "A" category (i.e., not relevant for novelty or inventive step). It discloses 45 exemplified compounds ranging activity of < 50 µM, especially < 5 µM in HCV NS3 protease time-resolved assay Structurally, the substituent 'M' disclosed in the compound is 1,1-difluro-butyl-2,3-eneoxy chain linked to pyrrolidine ring, which is in contrast with the teaching of the present invention. The Opponent has not identified any compound from WO '507.

Even after having knowledge of the molecule and the fact that WO '163 is not even a prior art, , the Opponent has failed as many of the critical substituents (for instance di fluoro butyl alkaline chain) are not even present. In conclusion, despite knowledge of the claimed compound and ignoring not only scientific and legal knowledge, the Opponent could still not arrive at the claimed compound, Glecaprevir.



The Learned Controller will appreciate that the Opponents have arbitrarily and in hindsight identified the said documents and/or compounds disclosed therein without any scientific reasoning as to why a person skilled in the art would select the said prior art compounds and be motivated to combine with other cited reference in complete disregard to the teaching of the said document as a whole.

The entire case of the Opponents is based on hindsight. It is evident that even after carrying out such a futile exercise, the Opponents have failed to arrive at the compound of present invention, Glecaprevir.

In view of the above we request the Learned Controller to set aside this ground of opposition

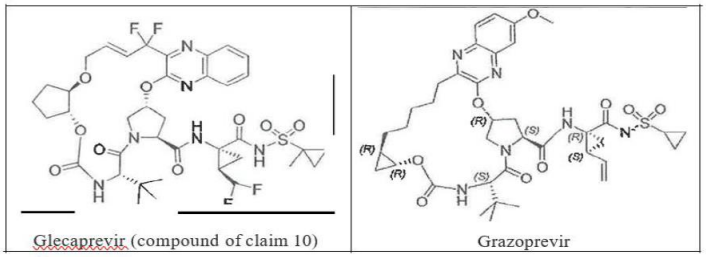
7. Ground (III): *Section 25(1)(f)* *- that the subject of any claims of the complete specification not an invention within the meaning of this Act, or is not patentable under this Act.*

7(a) Submission filed by the opponent-

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. On Section 25(1)(f), the Opponent submits as under:

(i) Glecaprevir, the compound claimed in claim 10, is a new form of grazoprevir, which is a known anti-HCV compound. Grazoprevir, also known as MK-5172, is a hepatitis C virus protease inhibitor acting against the NS3/4A protease targets. This compound is notably disclosed on page 1 and claimed in claim 1 of International application PCT/US2009/050915 (WO2010/011566), annexed as Annexure VIII) filed in the name of Merck & CO., INC. and lnstituto Di Ricerche Di Biologia Molecolare P. Angeletti S.P.A, and published on 28 January 2010, i.e. before the earliest claimed priority date of the impugned application (21 September 2010).

The chemical structures of glecaprevir and grazoprevir are represented below:



Glecaprevir (compound of claim 10)

Grazoprevir

(ii) The Hon'ble Supreme Court in Novartis AG vs Union of India & Others (AIR 2013 SC 1311) (hereinafter the 1'Glivec case"), observed "The amended portion of Section 3(d) clearly sets up a second tier of qualifying standards for chemical substances/pharmaceutical products in order to leave the door open for true and genuine inventions but, at the same time, to check any attempt at repetitive patenting or extension of the patent term on spurious grounds".

The Supreme Court interpreted "efficacy" as "therapeutic efficacy" stating that the "therapeutic efficacy" of a medicine must be judged strictly and narrowly.

"...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"

(iii) It is submitted that in pharmacology, intrinsic activity or efficacy refers to the ability of a drug to induce a biological response in its molecular target. Efficacy is defined as "the generation of a response from the drug receptor complex". Efficacy is that property intrinsic to a particular drug that determines how good an agonist the drug is.

(iv) Another useful and more detailed definition of efficacy is that provided in Tripathi K.D, "Essentials of Medical Pharmacology': 5th edition, Jaypee Brothers Medical Publishers Ltd, Page 37, lines 10-13 which broadly defines efficacy as "ability of the drug to activate (induce a conformational change in) the receptor consequent to receptor occupation."

(v) Both of the above definitions establish that a mere physical variant of an existing pharmaceutical product lacks the necessary quality of therapeutic efficacy which is a condition precedent to a known substance being considered patentable under the Act. It is also an established position of law that the term "efficacy" in Section 3(d) means therapeutic efficacy for pharmaceutical products.

(vi) It is a matter of record that glecaprevir (compound of claim 10) does not show any enhancement of therapeutic efficacy when compared with the

known efficacy of grazoprevir. On the contrary, glecaprevir has a lower clinical (i.e. in vivo) antiviral activity than grazoprevir as demonstrated in the citations and table below:

• "Potent Antiviral Activities of the Direct-Acting Antivirals ABT-493 and ABT- 530 with Three-Day Monotherapy for Hepatitis C Virus Genotype 1 lnfection patients with HCV genotype 1 infection" (pages 1546-1555) by Lawitz et al. (2015), which discusses the antiviral activity of the different protease inhibitors of HCV RNA. For reducing the HCV RNA level in the patients, a dosage within the range of 100 to 700 mg of NS3/4A inhibitor had to be administered. Glecaprevir falls under this specific category of protease inhibitors.

• "MK-5172: a second-generation protease inhibitor for the treatment of hepatitis C virus infection" (Pages 1-10) by Gentile et al., (2014)1 which mentions that patients with HCV genotype 1 infection were administered with 50 to 800 mg of MK-5172 to inhibit HCV RNA activity. The article also mentions that this category of protease inhibitors also overcomes the drawbacks of the first generation protease inhibitors.

	Mean decline in plasma HCV RNA level (log_{10} IU/ml)	*Reference*
Glecapravir	3.8 to 4.3 log10	Annexure XI: Table 2
MK-5172	5.38 log10	Annexure XII: paragraph 3.4

It should be noted that these results obtained in vivo, are representative of the clinical, i.e. real life data, for establishing the efficacy of the compounds, in comparison to experimental results obtained in vitro, e.g. with the replicon assays. Thus, these data are more reliable in comparison to the table presented in page 6 of the FER response filed by the Applicant herein vide a letter dated August 27, 2018.

Besides, claims 1-9 of the impugned application covers a wide variety of compounds within the scope of the broad Markush structure and claims that all the compounds covered have anti-HCV activity. However, the number of claimed variants appear to be disproportionate to what is actually disclosed and supported by pharmacological evidence as disclosed in the complete specification of the invention. Support for the alleged anti-HCV

activity of the claimed compound can be found on pages 122 and 123 of the impugned application.

The EC_{50} values of only few compounds are provided in the disclosure of the impugned application. In particular compounds of Examples 1, 2, 4, 5, 6, 8 and 65 falling in the scope of claim 1, when tested using different genotype replicon assays are indicated (refer to pages 122 and 123 of the impugned application). Other than this the impugned application does not provide evidence demonstrating that substantially all the compounds covered by claim 1 possess anti-HCV activity. It may thus be concluded that the impugned application fails to provide the evidence that all the compounds covered within the scope of formula (VII) has any anti-HCV activity at all. In light of the foregoing it is not possible to determine whether the claimed compounds show advanced therapeutic efficacy with respect to the compounds mentioned in the prior arts and such claims should be dismissed due to lack of inventive step.

Therefore, in light of the above, it is respectfully submitted that the impugned application claims a derivative of a known substance, and therefore the applicant has failed to discharge the onus of fulfilling the requirement under section 3(d) of the Act. Hence, the impugned application cannot be treated as a patentable invention and should be refused under Section 25(1)(f) of the Act.

7(b)(ii) Submission filed by the applicant-

The opponents have relied on the following documents to support their case on section 3(d).

Annexure	Document	Allege
VIII	WO2010011566A1	Glecaprevir is a new form of Grazoprevir, hence derivatives -No enhancement of therapeutic efficacy
IX	Burton L. L, Lazo J. G. et al, *"Goodman and Gilman's, The Pharmacological Basis of Therapeutics"*	Efficacy is defined as "the generation of a response from the drug receptor complex"

X	Tripathi K. D, *"Essentials of Medical Pharmacology"*	Efficacy is "ability of the drug to activate (induce a conformational change in) the receptor consequent to receptor occupation"
XI	Lawitz et al., (2016) *Antimicrobial Agents and Chemotherapy, 60: 1546-1555*	Antiviral activity of the different protease inhibitors of HCV RNA
XII	Gentile et al., (2014) *Expert Opin. Investig. Drugs, 23: 1- 10*	Patients with HCV genotype 1 infection were administered with 50 to 800 mg of MK-5172 to inhibit HCV RNA activity

❖ Ann-IX to Ann-X is considered merely to explain 'efficacy' as also admitted by Opponents.

❖ Ann-XI and Ann-XII are not valid prior arts (Post Publication documents)

❖ Ann-XI are considered to show the antiviral activity of different protease inhibitors, while Ann-XII is related to Grazoprevir, also known as MK-5172 having HCV activity.

CASE LAW

The applicant relies upon BMS vs BDR, DHC, CS(COMM) 27/2020 on 30 January 2020 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.

Section 3(d) bars the patentability of a new form of a known substance provided enhanced efficacy is shown. The law, for section 3(d) to apply in the first place, two criteria have to be satisfied.

(a) That the claimed invention is a new form of a known substance; and

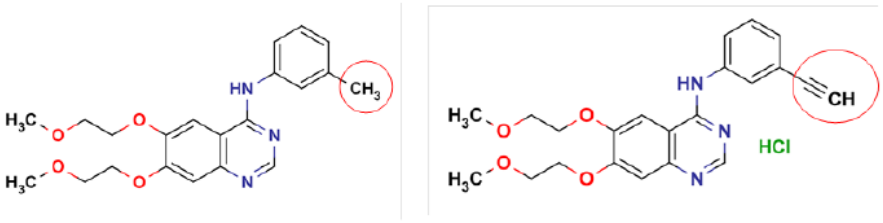
(b) That the said KNOWN SUBSTANCE should have KNOWN EFFICACY.

The NOVEL claimed compound 'Glecaprevir' is not the new form of a known substance nor salt, esters or polymorphs. There is no known substance at the priority date of the instant application.

It is not enough for Section 3(d) to be attracted to show that there is some known compound in the prior art which allegedly bears some structural resemblance to the claimed compound.

The compound Glecaprevir is structurally different from the compounds disclosed in the cited prior art.

The Division Bench of the Hon'ble Delhi High Court in Roche vs Cipla did not hold Erlotinib, the claimed invention as being a derivative of a prior art compound even when there was a high structural similarity. The court dealt with this issue under "INVENTIVE STEP" and NOT Section 3(d) and treated Erlotinib as a New Chemical entity.

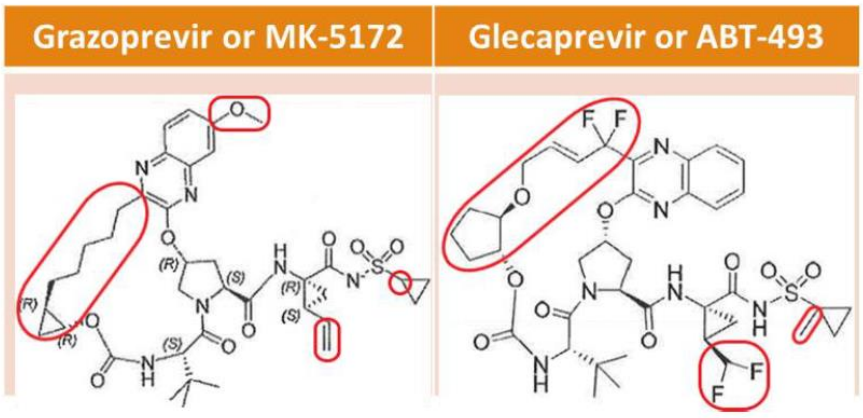


Example 51 of EP'226 | Erlotinib Hydrochloride

The term 'derivatives' in explanation part of Section 3(d) should not be confused with the term derivative ubiquitously used in chemistry. Concept of 'ejusdem generis'.

WO2010011566A1 (Ann-VIII) & Ann-XII

WO '556 - grazoprevir, also known as MK-5172, alleged to have similar therapeutic effect as HCV protease inhibitor. Grazoprevir and Glecaprevir are structural different compounds as illustrated below



Grazoprevir or MK-5172	**Glecaprevir or ABT-493**
7-methoxy on the quinoxaline ring	-
pentyl chain linked to cyclopropyl ring	1,1-difluorobutyl-2,3-ene-4-oxo chain linked
ethylene substituent	difluoro methyl substituent

-	Methyl substituent on the terminal cyclopropyl

The data presented by Opponents does not support the allegation

❖ Mere comparison of two different documents for antiviral activity

❖ Conditions considered for studies are different

❖ Data acquired for Grazoprevir is for 7-days of treatment, while for Glecaprevir is for 3- days of treatment.

❖ The comparison of decline in plasma HCV RNA level also does not support Opponents' allegation

❖ Glecaprevir has superior efficacy (10- to 50-fold) relative to MK-5172, particularly for HCV genotype 1a, 1b, and 3a mutants

	Mean decline in plasma HCV	**Reference**
Glecaprevir or ABT-	3.8 to 4.3 log10	Annexure XI (Table 2)
Grazoprevir or MK-5172	5.38 log10	Annexure XII (Para 3.4)

Grazoprevir is approved against GT-1, glecaprevir is a pan-genotypic inhibitor and is approved against all the genotypes (GT1–6), highlighting the biological significance of the subtle differences between these compounds. Cf. The Enzymes, vol. 50, 2021, Pages 301- 333 (doi.org/10.1016/bs.enz. 2021.09.004)

Comparison with the highly similar grazoprevir indicated the mechanism of GLE's drastic improvement in potency. (Abstract) On page 10, line 25 and 26 states GLE inhibits NS3/4A GT1a with a Ki at least 42-fold better than GZR. Cf. Jennifer Timm et al., Molecular and Structural Mechanism of Pan-Genotypic HCV NS3/4A Protease Inhibition by Glecaprevir, ACS Chem. Biol. 2020, 15, 2, 342–352 (doi.org/10.1021/acschembio.9b00675). The phrase "comparison with highly similar grazoprevir" is not in reference to the structure but to its mechanism of action.

In view of the above we request the Learned Controller to dismiss this ground of opposition.

8. Ground (IV) : Section 25(1)(g)- Lack of sufficient and clear description of the invention

8(a) Submission filed by the opponent-

Claims 1-9 of the unrevised claims asserted monopoly over a wide variety of compounds all of which claim to demonstrate anti-HCV activity. Those Markush formulae claimed a large number of compounds, all allegedly showing anti-HCV activity. The Opponent contended, inter alia, that whether all claimed variants of the Markush formula actually show anti-HCV activity cannot be precisely determined without undue burden of individually testing each of the compounds encompassed within the scope of such an extremely broad Markush structure. Further, the unrevised claims exemplified the synthesis of less than 297 compounds, irrespective of the corresponding general formula considered, while formula (VII) alone likely covered more than about 108 different compounds. Moreover, the unrevised claims only disclosed synthesis of around 297 compounds, without considering that formula VII alone encompasses about 100 different compounds. So, without providing sufficient clinical data for all the different compounds within the scope of Markush structure of Formula VII, the Opponent had submitted that it would be prejudicial to consider that all such compounds show anti-HCV activity. Under the revised claims of 31 December 2019, the sweep of compounds under claim is now narrower. Therefore, this ground is now pressed only to the extent that the disclosure(s) of the invention are not commensurate with the scope of the claims.

8(b) Submission filed by the Applicant-

At the hearing, the Opponents dropped the ground of lack of sufficiency under Section 25(1)(g) of the Indian Patents Act.

CONTROLLER ANANLYSIS AND OPINION-

Opinion of the Controller on the ground under Section 25(1)(e)

9. Following documents are relied upon by both the parties, as prior art, for inventive step analysis-

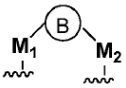
(1) WO2010132163A1 (hereafter referred as D1)

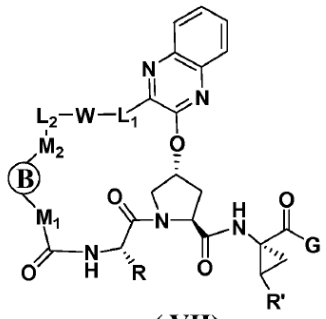
(2) WO2009064975A1 (hereafter referred as D2)

(3) WO2008057209 (hereafter referred as D3)

(4) WO2009108507A1 (hereafter referred as D4)

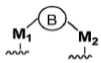
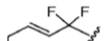
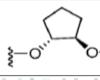
D1 is published on 18 November 2010 and is not considered as valid prior art document because it was published after the priority date of the present application which is 21 September 2010 derived from US patent application number 61/385058. US61/385,058 discloses the claimed compound in Table 1, Example 6, pages 10-11 (abridged) and 80 of the description as follows-

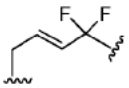
Representative compounds of the invention include, but are not limited to, the following compounds (example 1 to example 256 in Table 1) according to Formula VII wherein R, -L_2-W-L_1-,  , R' and G are delineated for each example in Table 1.

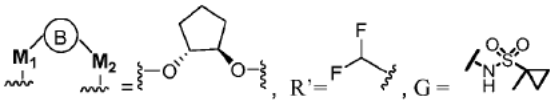


(VII)

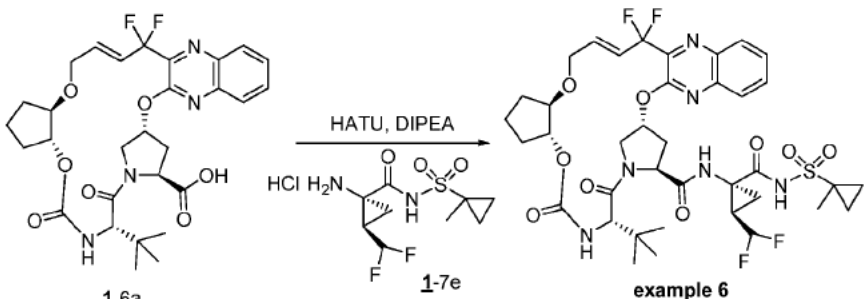
TABLE 1

Example #	R	-L_2-W-L_1-		R'	G
6.					

Example 6. Compound of Formula VII, wherein R =  , L_1-W-L_2=  ,



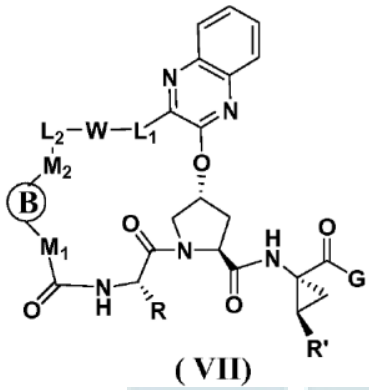
Step 6a



In the light of the said disclosure the claimed compound of the present invention is considered to be clearly disclosed in the priority document US61/385,058. Further the second priority document US61/499,994 dated 22 June 2011 also discloses claimed compound in Table 1, Example 6, pages 13-14 (abridged) and 88

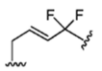
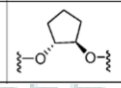
Representative compounds of the invention include, but are not limited to, the following compounds (example 1 to example 256 in Table 1) according to Formula VII wherein R, -L_2-W-L_1-,

, R' and G are delineated for each example in Table 1.



(VII)

TABLE 1

Example #	R	-L_2-W-L_1-		R'	G
6.					

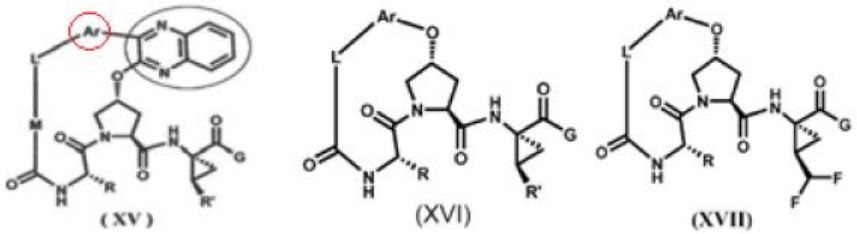
Hence in the present case the condition referred to in section 11(3)(a) of the Patents Act is applicable instead of section 11(3)(b) of the Patents Act and same is found to be met. Hence D1 is not considered as valid prior art for the claimed invention and not discussed herewith for analysis of inventive step.

D2 discloses macrocyclic compounds containing quinoxaline ring as HCV NS3 protease inhibitors (page 1, line 10-11). It discloses 1586 compounds of

a. Formula XV – Example 1 to 1506 in Table-1, page 17-129 (Not claimed)

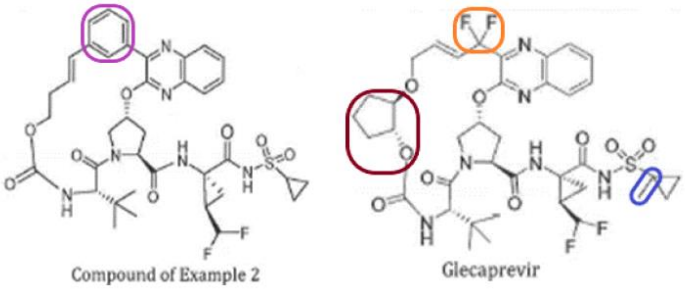
b. Formula XVI – Example 1507 to 1554 in Table-2, page 130-134 (Claimed)

c. Formula XVII – Example 1555 to 1586 in Table-3, page 134-137 (Claimed)



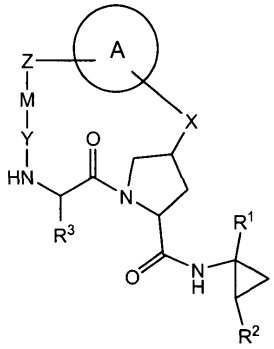
The opponent has primarily referred to Formula (XV) read with Example 2 and Formula (I), p. 4, read with Table I to III and has argued that said iterations map directly onto certain core elements and functions of the impugned application.

It is observed that compound of formula 2 is structurally different from the claimed compound as follows-

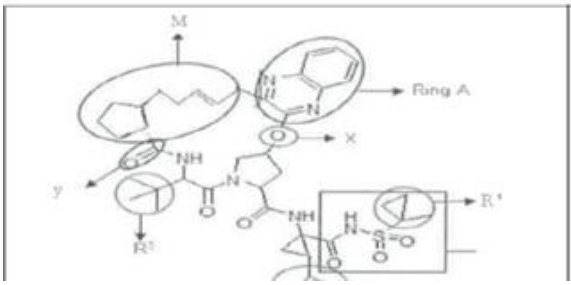


Further none of the claimed compounds 1507-1586 contains di-fluoro on alkene chain or methyl substituent on the terminal cyclopropyl ring and also the cyclopentyl oxy as envisaged in glecaprevir.

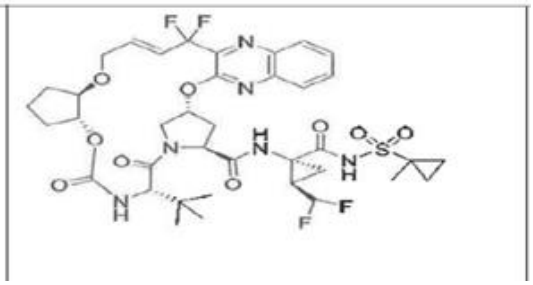
D3 discloses macrocyclic compounds of following formula (I) that are useful as inhibitors of the hepatitis C virus (HCV) NS3 protease, their synthesis, and their use for treating or preventing HCV infections.



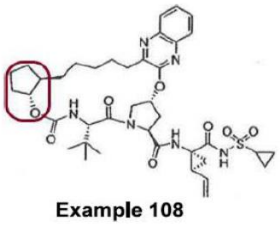
The opponent has stated that D3 offers three iterations [Formula (I), examples 108, 120 and 134 collectively] that map directly onto certain core elements and functions of the impugned application.



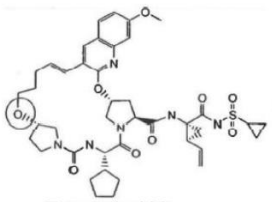
Compound as deduced from Formula(I) of D3



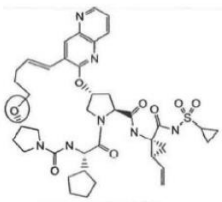
Glecaprevir (as claimed in claims 1 1 & 2 of the present invention)



Example 108



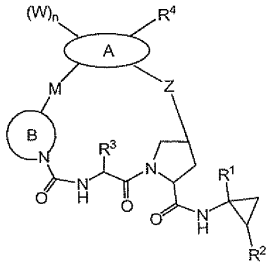
Example 120



Example 134

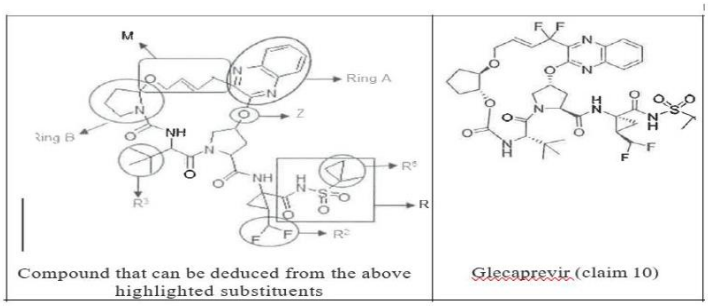
The scaffold of Example 108 is quinoxaline and the cyclopentyl ring is linked at 3rd position through pentyl chain and differs in its basic scaffold and M-chain. The scaffold in example 120 is 7-methoxyquinoline. The scaffold of example 134 is 1,5-napthyridine ring & M-chain is pyrrolidine ring linked through alkylene oxy chain (i.e., pentylene oxy chain). It is observed that compound of examples 108, 120 and 134 are structurally different from the claimed compound glecaprevir and there is no teaching in the D3 to motivate a person skilled in the art to modify said structures or pick specific substituents so as to prepare hypothetical compound as deduced by the opponent from formula (I).

D4 discloses class of macrocyclic compounds of following formula (I) that are useful as inhibitors of viral proteases, particularly the hepatitis C virus (HCV) NS3 protease.



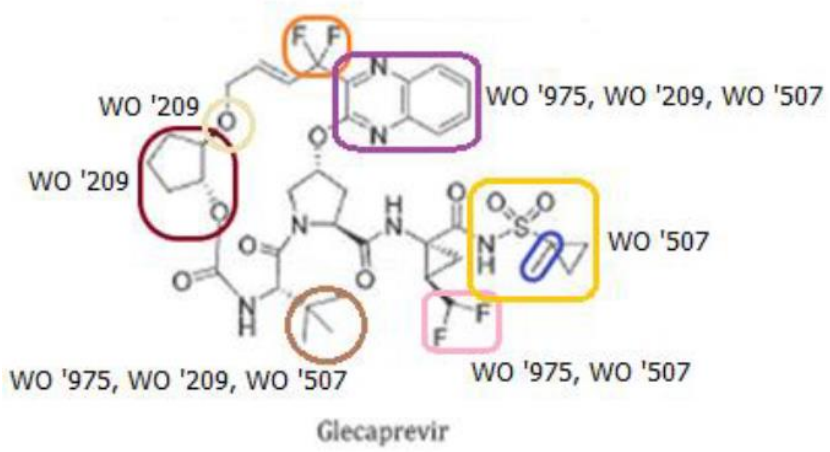
(I)

The opponent argued that D4 provides iteration [Formula (I)] which offers an alternate path to the –O– linkage connecting a cyclopentyl ring with the alkene chain. Further the opponent discloses a compound deduced from formula I and compared it with claimed compound glecaprevir.



The applicant has argued that the opponent has not identified any compound from D4. It is observed that compound deduced from formula (I) is a hypothetical compound, which is again structurally different from the claimed compound glecaprevir.

The Opponent has relied on various parts of chemical structures disclosed in the cited prior art documents D2 (WO '975), D3(WO '209) and D4('507) and has argued that by combining said structural parts a person skilled in the art can reach the claimed compound structure. The applicant has summarized said approach and represented same as follows-



As can be seen from above comparison, even after combining various parts of structure as disclosed in D1-D4 the opponent has failed to arrive at the complete structure of claimed compound of the present invention i.e. glecaprevir. Hence primarily the opponent has failed to create the claimed compound structurally from the compounds disclosed in the cited prior art documents. Further the opponent has also not able to provide any substantial argument to show as to why a person skilled in the art would pick up specific parts of the structure from the known compounds and combines them together to reach the claimed compound glecaprevir. The opponent has completely failed to show any reason or motivation in the prior

art which teaches a person skilled in the art to carry out such combination of substituents and structural fragments of known compounds disclosed in the cited prior art documents in order to achieve the properties that the present invention was seeking with a reasonable expectation of success. Therefore the subject matter of claims 1-2 is considered to involve an inventive step under section 2(1)(ja) of the Patents Act.

Hence I am of the opinion that ground under section 25(1)(e) of the Patents Act is not valid.

Opinion of the Controller on the ground under Section 25(1)(f)

10. The opponent has relied on following documents under this ground-

- WO2010/011566A1 (hereafter referred as D5)
- Tripathi K. D, "Essentials of Medical Pharmacology" 5th edition, Jaypee Brothers Medical Publishers Ltd, Page 37, lines 10-13 (hereafter referred as D6)
- Lawitz et al., (2016) Antimicrobial Agents and Chemotherapy, 60: 1546- 1555 (hereafter referred as D7)
- Gentile et al., (2014) Expert Opin. Investig. Drugs, 23: 1-10 (hereafter referred as D8)

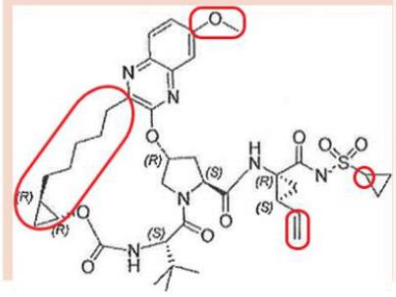
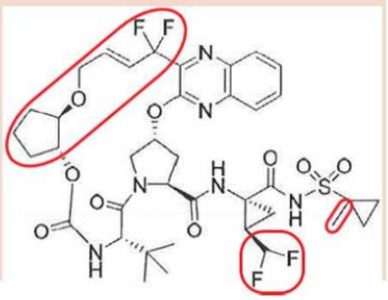
Section 3(d) of the Patents Act, 1970 read as follows-

> "*the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of the substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant.*
>
> *"Explanation—For the purposes of this clause, salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy".*

The opponent has primarily argued that the claimed invention is mere discovery of a new form of a known substance which does not result in the

enhancement of the known efficacy of the substance. To apply said clause pre condition is existence of a known substance with a known efficacy and then one need to show that claimed substance is new form of such known substance. Referring to D5 the opponent has argued that claimed compound glecaprevir is new form of a known compound grazoprevir which is a known anti-HCV compound. Further the opponent has referred to D6 for definition of "efficacy" and two post publications documents D7 and D8 to show antiviral activity of grazoprevir.

If one sees the chemical structures of glecaprevir and grazoprevir it's clear that there are substantial differences in the structures of two compounds which are aptly summarized by the applicant as follows-

Grazoprevir or MK-5172	Glecaprevir or ABT-493
	

Grazoprevir or MK-5172	**Glecaprevir or ABT-493**
7-methoxy on the quinoxaline ring	-
pentyl chain linked to cyclopropyl ring	1,1-difluorobutyl-2,3-ene-4-oxo chain linked to cyclopentyl ring
ethylene substituent	difluoro methyl substituent
-	Methyl substituent on the terminal cyclopropyl ring

In the light of the referred structural differences between two compounds which not only includes difference in substituents attached to basic skeletal structure but also includes difference in basic skeletal structure of two compounds, I am of the opinion that grazoprevir can not be considered as known substance for the claimed compound glecaprevir accordingly there is no relevance of the comparison of efficacy of said two compounds for the purpose of determining enhancement in efficacy as per section 3(d) of the

Patents Act. Therefore the subject matter of claims 1-2 does not fall within the scope of section 3(d) of the Patents Act.

Hence I am of the opinion that ground under section 25(1)(f) of the Patents Act is not valid.

Opinion of the Controller on the ground under Section 25(1)(g)

11. The ground of insufficiency of disclosure under section 25(1)(g) is primarily directed against Markush claims 1-9 which were deleted by the applicant while filing the reply to the pre-grant opposition. Currently there are two claims on the record which relates to structure of the compound Glecaprevir and pharmaceutically acceptable salt thereof for which sufficient and clear support is provided in the description hence I am of the opinion that ground under section 25(1)(g) of the Patents Act is not valid.

CONCLUSION:

12. After thorough and careful consideration of the pre-grant opposition filed by all the opponents under section 25(1) of the Act, statements and evidences produced by all the opponents and the applicant before and at the time of hearing, arguments presented by all the opponents and the applicant during hearing, written submissions by all the opponents and the applicant filed after hearing and in view of my above stated analysis and findings I reject the pre-grant representation as none of the grounds, raised therein, were found to be valid. Therefore, I hereby proceed with the grant of patent for the instant application number 2891/DELNP/2013 with two (02) claims.

The case is hereby disposed of under section 25(1) of The Patents Act, 1970 (as amended) and corresponding rule 55 of The Patents Rules, 2003 (as amended). There is no award of costs to either party.

Dated this 29th day of January 2024

-Sd/-

(DR. ROHIT RATHORE)

Deputy Controller of Patents & Designs