

The Patent Act 1970 (as amended)
Section 25(1)

In The Matter of
Patent Application No. 1310/DELNP/2013
And

In The Matter of

A Pre-Grant opposition to the grant of a Patent thereon under section 25(1)

AbbVie Manufacturing Management Unlimited Company Applicant

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

Present on behalf of the Applicant (through Anand & Anand Advocates)

Ms. Archana Shanker
Mr. Devinder Rawat and
Ms. Vashima Miglani

Present on behalf of the Opponents

Mr. Anand Grover
Ms. Ramya Sheshari

ORDER

1. The patent application no. 1310/DELNP/2013 was filed on 12/02/2013 by the applicant entitled "ANTI VIRAL COMPOUNDS". As per the provision under section 11-A of Patents Act, the said application was published on 26/09/2014.
2. A Pre-Grant representation under section 25(1) of the Patent Acts was filed against the grant of the patent application no. 1310/DELNP/2013.
3. Details and important dates of Application filed by AbbVie Manufacturing Management Unlimited Company for grant of the Patent are mentioned herein below:

Application no.	1310/DELNP/2013
Applicant	AbbVie Manufacturing Management Unlimited Company
Date of Filing	12/02/2013
International Application Number	PCT/US2011/056045
Title of Invention	ANTI VIRAL COMPOUNDS
Request for Examination Number	9851/RQ-DEL/2014 dated on 06/10/2014
Publication date u/s 11A of Patents Act	26/09/2014
FER issued date	07/12/2017
Date of Response to FER	05/06/2018
Opposition filed by	Delhi Network of Positive People (DNP+) and Initiative for Medicines, Access & Knowledge, Inc. (I-MAK) on 21/07/2018
Reply statement filed by Applicant	24/04/2023
Additional documents filed by the Applicant	11/12/2025 17/02/2026
First Hearing scheduled	18/12/2024
Second Hearing scheduled	24/02/2026
Hearing Date	16/06/2026

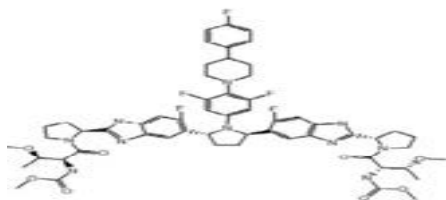
4. GROUNDS OF PRE-GRANT OPPOSITION TAKEN BY OPPONENT

The impugned application was opposed on the following grounds by the opponent mentioned under Section 25 (1) of the Indian Patents Act:

- Section 25(1)(a): that the applicant for the patent or the person under or through whom he claims, wrongfully obtained the invention or any part thereof from him or from a person under or through he claims;
 - Section 25(1)(i): that in case of a convention application, the application was not made within twelve months from the date of the first application for protection for the invention made in a convention country by the applicant or a person from whom he derives title;
 - 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;
 - 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.
5. The merits of the pre-grant opposition has been reviewed in the light of the amended set of claim 1 submitted along with post hearing written submissions on 30/06/2026. The amended set of claim is recited as under:

We Claim:

1. Methyl {(2*S*,3*R*)-1-[(2*S*)-2-{5-[(2*R*,5*R*)-1-{3,5-difluoro-4-[4-(4-fluorophenyl)piperidin-1-yl]phenyl}-5-(6-fluoro-2-{(2*S*)-1-[*N*-(methoxycarbonyl)-*O*-methyl-L-threonyl]pyrrolidin-2-yl}-1*H*-benzimidazol-5-yl)pyrrolidin-2-yl]-6-fluoro-1*H*-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methoxy-1-oxobutan-2-yl}carbamate



acceptable salt thereof.

or a pharmaceutically

The documents relied upon by the Opponents in support of the ground of lack of inventive step, together with their publication dates, are as follows:

Sr. No.	Document	Publication Date
1	US2011/0207699 ("US'699")	25 August 2011
2	WO2010/144646 ("WO'646")	16 December 2010
3	Wagner et al., J. Med. Chem. 61:4052 (2018)	13 April 2018
4	US2010/0267634 ("US'634")	21 October 2010
5	WO2010/091413 ("WO'413")	12 August 2010
6	US2010/0074863 ("US'863")	25 March 2010
7	WO2009/003009 ("WO'009")	31 December 2008
8	US2009/0036444 ("US'444")	5 February 2009

Opponent's Submission on the Impugned Application

The impugned application titled “**Antiviral Compounds**” is a national phase application from PCT/US2011/056045 (WO/2012/051361) filed on 12th October 2011. The Indian application no.1310/DELNP/2013 with date of filing **12 February 2013** initially included 22 claims however after the issuance of First Examination Report by the IPO, the applicant to comply with the objections of FER amended the claims and restricted them to only 3 claims.

Valid Priority Date of the Application:

The impugned application derives priority from four US applications. The opponent submits since the applicant has restricted their application only to 3 claims and have given up remaining 19 claims (Refer to Pre-grant Opposition document @ para no. 7.2.2 & 7.3.3 at PDF page no.8). The applicant cannot derive a priority date in respect of the claims of priority applications which were given up.

In view of the cancellation of those 19 claims the date of filing of priority applications pertaining to cancelled claims cannot provide a priority date for the impugned application since each inventive feature will have a different priority date. The compound in amended claim 1 was first disclosed in the priority document US61/446,800. However, the earlier two priority applications US12/903,822 and US12/964,027 pertain only to markush structure, general method of preparation and possible list of multiple compounds of NS5A class of inhibitors. They do not explicitly disclose claimed compound of Example 3.52 (Pibrentasvir) of claim 1. Therefore, the effective priority date according to opponents is 25 February 2011, of priority patent application US61/446,800. Thus, any document published prior to this date is considered to be a valid prior art document.

Priority Application Number	Priority Date	Claimed Compound Pibrentasvir Covered
US12/903,822	13 October 2010	No
US12/964,027	09 December 2010	No
US61/446,800	25 February 2011	Yes
US13/100,827	04 May 2011	Yes

The Applicant submitted since the amended claimed compound is fairly based on the matter disclosed in the priority specification, they are entitled for earliest priority application US12/903,822 dated 13 October 2010. The Opponents brings to the attention regarding a case law **Rallis India Ltd. v. Controller of Patents and Designs, 2025**, wherein it was held by the Madras High Court that the **Controller has to examine the “fairly based” contention** raised by the appellant stemming from a priority application and provide a reasoned order in terms of why a prior art document was not considered while assessing the validity of the application based on the disclosures found in the said document. The judgment is annexed herein as Annexure A.

Amended Claims 2 and 3 Not Maintainable:

Claim 1 is an independent claim that covers the main compound of example 3.52 (Pibrentasvir) (as filed claim 15), claim 2 is also an independent Claim covering a pharmaceutical composition comprising the compound (as filed claim 16) and claim 3 is dependent on claim 1 & 2 which relates to use of compound in treating HCV patients (newly added).

Claim 2 covering the pharmaceutical composition does not indicate what the claimed composition comprises. It is vague and the claim fails to spell out clearly the ratio of ingredients including that of the compound and the types of components included in the claimed composition. Further no

supporting examples depicting the constituents of the claimed composition is provided in the specification.

Claim 3 is method of treatment which is also noted by the Patent Office and thereby should not be allowed. The Opponent submits claim 2 & 3 should be not considered at all and rejected. Therefore, the Opponents will submit arguments only on grounds of opposition only against **Claim 1**.

APPLICANT'S SUBMISSION

CLAIM REVISIONS

It is submitted that claims 2 and 3 have different scope than claim 1. While claim 1 is in relation to the compound and its pharmaceutically acceptable salt, claim 2 is a narrower claim for free base and is dependent on claim 1. Claim 3 is an embodiment that is an application claim of a claimed compound and thus has the same inventive concept.

The Applicant drew the attention to pages 412-415 of the patent specification where extensive details of the pharmaceutical composition have been provided. A person skilled in the art based on the common general knowledge and their qualifications can easily derive a pharmaceutical composition once having knowledge of the compound of the present application. There is no requirement under law to provide working example for composition for a claim to be included in that respect.

Pursuant to the directions at the hearing under Section 14 of the Indian Patents Act held on June 16, 2026, the Applicant only with a view to expedite the prosecution of the application has deleted claims 2 and 3. The deletion of the said claims do not impact the scope of claim 1 and the said claim covers free base, as well as any composition that includes and comprises pibrentasvir and or its salts.

ABOUT THE INVENTION- PIBRENTASVIR

The present invention discloses inhibitors of HCV replication and therefore are useful for treating HCV1 infection. The inventors of the present invention unexpectedly found that compound of claim 1 showed significantly improved activities against different HCV genotypes 2 and variants.

The compound of claim 1 has been assigned the INN (international nonproprietary name) of “**pibrentasvir**” by WHO 2016 with an internal code provided by the Applicant as being ABT-530. A copy of the WHO drug information of 2016 has been filed with the reply statement is enclosed as Annexure C. For the purpose of the present proceedings, the claimed compound will hereinafter referred to as “**pibrentasvir**”.

Pibrentasvir Structure

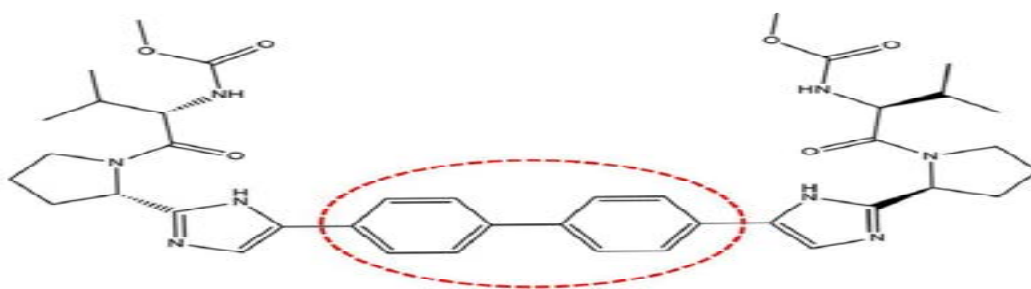
As per claim 1, the different moieties of pibrentasvir are provided below. The same color codes represent each of the said moiety



Details of research in the specification by the inventors

The Applicant during the hearing drew the attention to the patent specification in order to demonstrate the nature of research that led to the present invention through a series of structural modifications that resulted in a new compound altogether. Reference in this regard is made to pages 2-15 of the patent specification wherein the Applicant briefly discussed the following:

- i. Several prior art documents that have been discussed that have compounds having a dimeric or dimer-like structure to improve interaction with NS5A protein (page 2-4 of the specification.
- ii. Tables 1-4 compares the anti-viral activities of different NS5A inhibitors of the prior art documents.
- iii. Once such molecule is Daclatasvir (BMS 790052) described in WO2010/096462 that employs a bi-phenyl linker between the imidazole moieties as shown below:



- iv. Table 1 provides the EC₅₀ value of daclatasvir with other compound wherein the bi phenyl linker of daclatasvir was replaced with other linkers.
- v. The said data demonstrates that changing a bi phenyl linker as provided in daclatasvir significantly reduces the activities of the compound against HCV genotypes.
- vi. Table 2 discussed compounds containing unsubstituted benzimidazole which are then replaced with halo substituted benzimidazole. The results in table 2 clearly demonstrate that

compound comprising substituted benzimidazole had worse activity against HCV viruses. This is opposite to the research that led to pibrentasvir

vii. Table 3 compared compounds with different linkers between benzimidazole moieties. The results demonstrate that compounds containing pyrrolidinyl linker show worse anti HCV activity.

viii. Table 4 shows that when the nitrogen atom in the pyrrolidinyl linker is substituted with carbocycle or heterocycle, the anti-viral activities of the compound can be drastically improved. Table 5 shows the anti-HCV activities of compounds in which the pyrrolidinyl linker is substituted with substituted carbocycle or heterocycle.

Conclusion based on prior art discussed in the complete specification: Counterintuitive Nature of Pibrentasvir

(i) The prior art consistently teaches away from pibrentasvir's structural features, demonstrating inventive choice.

(ii) **Biphenyl Linker (Table 1):** Daclatasvir employs a biphenyl linker between imidazole moieties. Table 1 shows that replacing this linker with alternatives significantly reduces anti-HCV activity. The teaching of the prior art was to retain the biphenyl linker. Pibrentasvir departs from this teaching, and does not include biphenyl linker between imidazole moieties which is demonstrating an inventive choice.

(iii) **Benzimidazole Substitution (Table 2):** Table 2 demonstrates that fluorine substituted benzimidazole compounds exhibit worse anti-HCV activity than unsubstituted benzimidazole. The prior art teaches away from the fluorine substituted benzimidazole present in pibrentasvir.

(iv) **Pyrrolidinyl Linker (Tables 3–4):** Table 3 shows that compounds with an unsubstituted pyrrolidinyl linker have substantially reduced anti-HCV activity. However, Table 4 reveals that substitution of the pyrrolidinyl nitrogen with a carbocycle or heterocycle dramatically improves activity.

The Applicant wishes to place the following on record:

(i) At the hearing, the Opponent did not press for the grounds under Section 25(1)(a) and Section 25(1)(i).

(ii) No arguments were made by the Opponent at the hearing as to why the Applicant was not entitled to the priority date of October 13, 2010, based on US2012/903622 in view of Section 11 of the Indian Patents Act.

(iii) There are **no pleadings** in relation to US2010/0267634 in the opposition statement and therefore no arguments/submissions in relation to this document can be entertained.

(iv) US2011/0207699, WO2010/144646, Wagner *et al.* and US2010/0267634 are not prior arts for inventive step.

APPLICANT'S SUBMISSION

Priority date entitlement- Fairly disclosed Section 11 of the Indian patents Act

It is submitted that the Applicant is entitled to the earliest priority date of October 13, 2010. IN' 1310 is based on 4 US applications.

For being entitled to the earliest priority date, the Applicant has to demonstrate that pibrentasvir is fairly disclosed and can be derived from US application (US12/903,822) from which priority is claimed.

The Opponent has conveniently avoided the expression “**fairly based**” used in Section 11 of the Indian Patents Act and attempted to confuse the Controller to suggest that the disclosure of the claims in the PCT / Indian Application has to be identical to the US priority applications to be entitled to the priority date, which is contrary to law.

UK Patents Act 1949 and Indian Patent law similar: In order to explain the term ‘fairly based/disclosed’ and Indian law is similar to Section 5(2) of the U.K. Patents Act 1949, the Applicant submits that the provision for claiming the priority of an application in India (under section 11 of the Patents Act 1970) is similar to the priority claiming provision under section 5(2)5 of the U.K. Patents Act 1949 (Unamended) (enclosed). Additionally, there have been no amendments to section 11 of the Patents Act 1970 so far. Hence, reliance on UK case law.

In *Novartis AG and Ors. v. Natco Pharma Limited*, 2021: DHC:4143, 2022 (89) PTC 1 (Del) (enclosed), the Hon’ble Justice C. Hari Shankar, at paragraph 11.4, held that foreign judgments may be relied upon where there is no Indian precedent and the relevant statutory provisions are similar across the two jurisdictions.

- i. there are no precedents in India and
- ii. when two jurisdictions share similar statutory provision.

The Opponent has confused and conflated the expressions “Fairly based” and specific disclosure/ identical disclosure:

(i) The threshold for priority entitlement in India is extremely low as opposed to other jurisdictions particularly under the UK Patent Act of 1977 and EP convention that requires clear and unambiguous disclosure.

(ii) The term ‘fairly based’ does not require an **exact or literal disclosure** of the claim in the earlier/priority specification. Instead, it demands that the claim be reasonably and adequately supported by the disclosure contained in the priority specification. The claim must be grounded in the original disclosure in a way that a person skilled in art can derive the claim without introducing new matter beyond what was initially disclosed.

(iii) “*Fairly based*” means that the claim must be supported by the disclosure in a manner that is fair and reasonable, not necessarily an exact match but a clear and adequate basis in the earlier specification. “Fairly based means that the claims in a patent application must be supported by the information disclosed in the specification, ensuring the **claims don't go beyond what's described**.”

(iv) “Enabling disclosure,” on the other hand, means the specification must provide sufficient details for a person skilled in the art to make and use the invention without undue experimentation and is a test for anticipation.

(v) The Applicant relies on the following commentaries/case law:

a) Paragraphs 2-109 of T.A. Blanco-White (enclosed)

“2-109 A claim that sets out precisely what is to be found in a provisional specification, or a set of priority documents is necessarily fairly based thereon. Accordingly, the question of fair basing has three aspects:

- (i) claims that are broader than what the priority document foreshadows, generalising or omitting features from it;
- (ii) claims that are narrower, restricting the features foreshadowed or adding new limitations; and
- (iii) claims that render explicit what is at most implicit in the priority documents.

b) Patent Law by P. Narayanan (Fourth edition): 5-07 (enclosed)

"5-07 Meaning of "fairly based". The priority date of a claim in a complete specification will be the date of filing of the provisional specification if the claim is fairly based on the matter disclosed in the provisional specification. The question therefore arises what is the meaning of the phrase "fairly based" in this context. While discussing the corresponding provisions under the U.K Law, Lloyd-Jacob, J. observed:³ "It seems to me that there is a threefold 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?" The term "broadly" carried the meaning of "in a general sense" such as would be exemplified by a statement in the provisional that reaction products were dissolved in hot water where the complete specification introduced a specific temperature range.'

In *Letraset Ltd. v Rexel Ltd.* it is stated that the decision on fair basis "must be directed to giving the patentee a fair and reasonable monopoly having regard to his disclosure and at the same time to ensure that, as for example by the manipulation of dates, the public are not improperly prejudiced." In *UCB's Application*, it was observed that the question to be considered is whether the invention in the claim under consideration "can as a matter of substance be seen to be derived from and based on the disclosure in the provisional, even if it is not specifically disclosed". The underlying principle in these cases would appear to be that the Tribunal will not seek to be astute to deprive an Applicant of his claimed priority by the harsh application of linguistic or legal canons, but will seek to interpret the priority document in the way in which it may be interpreted by the notionally skilled but unimaginative man seeking to make an intelligent appreciation of the teaching afforded him by the disclosure.

"The claim in a patent must not go beyond the disclosure in the specification"

c) Mond Nickel company Ltd.'s application for a patent [1955] (enclosed)

"...[T]he priority date of the Applicants' claims is to be determined by reference to Sec. 5 (2) of the 1949 Act which enacts that in the case of a complete specification filed in pursuance of an application accompanied by a provisional specification the priority date of a claim will be the date of filing of the application if the claim is "fairly based" on the matter disclosed in the provisional specification. The interpretation of these words, which are new in Patent legislation, presents some difficulty, but it seems to me that in determining this issue, regard should be had

to the statutory requirements which must be fulfilled in the two kinds (provisional and complete) of specification.

The provisional specification (Sec. 4 (1)) has only to describe the invention. On the other hand the complete specification (Sec. 4 (3)) must:-

(a & b) particularly describe the invention and the best method for performing the invention which is known to the Applicant;

(c) end with a claim or claims defining the scope of the invention claimed.

Thus, it may fairly be assumed that for priority claiming at that is required is that the priority document may describe the invention in general rather than specific terms, and the Applicant is not required to define the scope of the invention at that stage.

d) Letraset Ltd Vs Rexel Ltd [1974] RPC 175 a similar issue arose and the Court held [refer page no 194-197] (enclosed)

“The question of priority date depends primarily on the provisions of section 5 of the Act, subsection (2) of which reads:

Where the complete specification is filed in pursuance of a single application accompanied by a provisional specification

... and the claim is fairly based on the matter disclosed in that specification, the priority date of that claim shall be the date of filing of the application”

The Court held that assessing whether a complete specification is "fairly based" on a earlier specification (provisional or complete) requires a threefold inquiry:

(i) Whether the alleged invention is broadly described in the provisional specification. (GENERAL DESCRIPTION)

(ii) Whether there is anything in the provisional specification inconsistent with the invention as claimed. (CONSISTENCY)

(iii) Whether the claim includes a feature as a characteristic of the invention that is wholly silent in the provisional specification. (NEW ESSENTIAL FEATURES)

Applying the above test, the Applicant submits that Pibrentasvir is fairly based on the matter disclosed in US Patent Application No. US12/903,822 dated October 13, 2010, as required under Sections 11(2) and 11(3) of the Indian Patents Act.

Markush Substituents			
	Pibrentasvir substituents	As filed claims (1-22)	Priority Document US'822 Exemplified
X	Pyrrolidine	Claim 1, Claim 4, 5, 6, 7, 8, 9, 10	Example 5.11 (Page 286)
L1/L2	Bond	Claim 1	
A/B	Benzimidazole	Claim 1, Claim 4, 5, 6, 7, 9	
Y/Z	Proline + threonine	Claim 1	
L3	Bond	Claim 1, 4, 12	Example 5.11 (Page 286)
D	Difluoro substituted with piperidin further substituted by 4-fluorophenyl	Claim 1, 4, 12	

OPPONENTS SUBMISSION

Amended Claim 1 is not patentable under Section 25(1)(e) due to lack of Inventive step:

The Opponents submit that the amended claim 1 covering the compound in the impugned application do not possess inventive step. The applicant has failed to submit supporting data and detailed experimental results that clearly demonstrate that Pibrentasvir possess anti-HCV activity in the specification. The efficacy data cited at page no.406 and 407 of the impugned specification using different HCV replicon assays also do not mention the compound of Example 3.52 as claimed in claim 1.

Further, the opponents submit that although the applicant has submitted in their response to pre-grant opposition extensive data about the anti-HCV activity of the compound Pibrentasvir in comparison to other compounds there is no indication as to when this data was generated and it is also not supported by any affidavit of an expert who generated the data. (Refer to Pre-grant Opposition document @ para no. 7.3.1 & 7.3.2 at PDF page no.9).

It is submitted that it is settled law that the data should be contemporary and should be available on the same date as that of the filing of the application. This is supported by the IPAB order of Novartis matter refer to page no.108 and 109. The judgment is annexed herein as **Annexure B**.

The extract from order is reproduced below

Can it make out a case of patent by providing data at a later date on efficacy?

*“A patent is granted on the basis of its full disclosure of the invention in the specification furnished on the priority date of the application. Even an amendment is also not allowed in the specification which in substance is not disclosed therein (see Section 59). **The patent law debars an Applicant a grant of patent for belated discovery of a new thing which is not disclosed which may or may not be pivotal in determining patentability. Thus, the Appellant is not entitled to make out a case for patent in its favour by importing a new matter in the specification which was later on discovered/established. The patentability, therefore, if any, will have to be established on the basis of original disclosure contained in the specification.**”*

The Opponents, therefore, submit that the applicant has not submitted any **effective data explicitly proving the efficacy of the claimed compound** and any data coming after the filing of the application which is *post facto* is inadmissible.

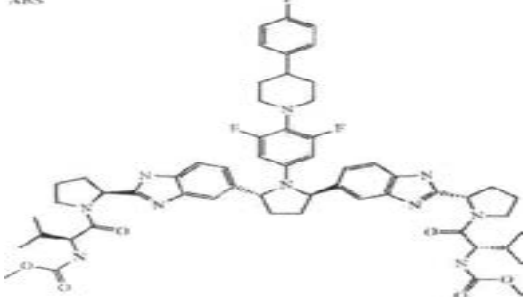
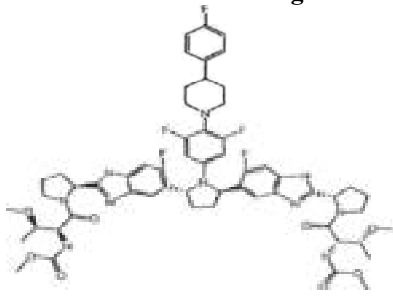
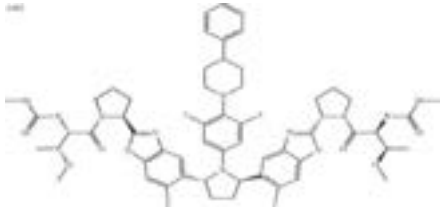
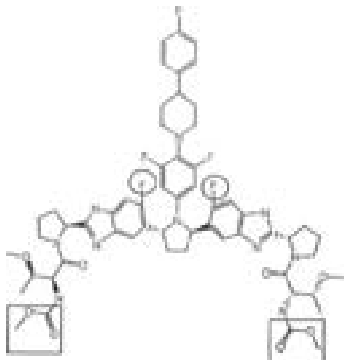
Amended Claim 1 is not patentable under Section 25(1)(e) due to obviousness

Claim 1 of the impugned application is obvious in light of the cited prior art documents. The opponent submits US patent application No. US2011/0207699 annexed as **annexure VII** (hereafter the '699 application, refer to Pre-grant opposition Annexure Part 2, @ PDF page no.74) filed by Abbott Laboratories), was published on 25 August 2011, i.e. before the effective date of the impugned application (12 October 2011). This application relates to compounds for inhibiting replication of HCV, as well as compositions comprising these compounds and methods of using these compounds to treat HCV (refer to specification at paragraph [0002]). The '699 application discloses compounds with a strong structural resemblance with **Pibrentasvir** and constitutes a promising **starting point for a development** leading to Pibrentasvir for a person skilled in the art. In particular, the compound of **Example 3.42 (see internal page 227 of**

the '699 **application** @ Annexure Part 2 PDF page number 301 and 302), has the same central core as **Pibrentasvir** and **similar lateral chains**.

The claimed compound when compared with the compounds of example 3.42 of '699 application reveals overlapping structures, with plausible structural modifications to the markush structure and both claimed compound & example 3.42 compound also exhibit similar HCV activity with EC50 value less than 0.1nM. (**see internal page 227** of the '699 **application** @ Annexure Part 2 PDF page number 301 and 302)..

Another compound of example 4.38 (**see internal page 250** of the '699 **application** @ Annexure Part 2 PDF page number 324) also possess similar structural similarities with Pibrentasvir. It is noted that it has exact same lateral chains as seen in Pibrentasvir, wherein Pibrentasvir comprises threonine in the N-methoxycarbonyl amino acid chain and fluoro-substituted benzimidazole rings.

US2011/0207699 (Annexure VII)	Impugned Application Compound
Example 3.42 Does not include fluorine atom at  benzimidazole ring	Example 3.52 (Pibrentasvir) is substituted by fluorine atom at Benzimidazole ring 
Example 4.38 comprises valine in N-methoxycarbonyl amino acid chain. 	Example 3.52 comprises threonine 

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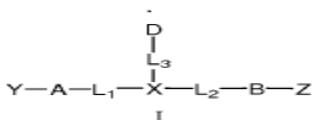
A person skilled in the art, working on developing alternative DAAs in same class of drugs is equipped with the prior knowledge of the markush structure with multitude of compounds disclosed in '699 application. The PSA would have considered the compounds disclosed in the '699 application as the starting point and the possibility of arriving at claimed compound Pibrentasvir cannot be ruled out.

Further, the modification of amino acids substitutions with halogens and evaluation of the activity of the modified compound constitute routine experiments in the development and optimization of the pharmaceutical compounds. Accordingly, the selection of threonine in place of valine in the N-methoxycarbonyl amino acid chain and addition of fluorine atom in each of the benzimidazole ring from the '699 application is already available. Therefore, the Opponents submit the claimed compound is obvious and not inventive.

The Opponents further submit that WO/2010/144646 annexed as **annexure VIII** (hereafter the '646 application, refer to Pre-grant opposition Annexure Part 2, @ PDF page no.376) filed by Abbott Laboratories, was published on 16 December 2010, i.e. before the effective date of the impugned application (25 February 2011). The Opponents submit the impugned application relates to compounds which are DAA and belong to HCV NS5A class of inhibitors. The NS5A inhibitors compounds for use in the treatment of HCV infection were already known at the effective date of impugned application.

The '646 application relates to compounds effective to inhibit replication of HCV as well as composition and methods of use comprising these compounds for use in the treatment of HCV infection. The '646 application discloses compounds derived from the following general markush formula (I) refer to claim 1 of '646 application below

A compound of Formula I, or a pharmaceutically acceptable salt thereof,



wherein:

X is C3-C12carbocycle or 3- to 12-membered heterocycle, and is optionally substituted with one or more RA;

L1 and L2 are each independently selected from bond; or C1-C6alkylene, C2-C6alkenylene or C2-C6alkynylene, each of which is independently optionally substituted at each occurrence with one or more RL;

L3 is bond or -LS-K-LS'-, wherein K is selected from bond, -O-, -S-, -N(RB)-, -C(O)-, -S(O)2-, -S(O)-, -OS(O)-, -OS(O)2-, -S(O)2O-, -S(O)O-, -C(O)O-, -OC(O)-, -OC(O)O-, -C(O)N(RB)-, -N(RS)C(O)-, -N(RB)C(O)O-, -OC(O)N(RB)-, -N(RB)S(O)-, -N(RB)S(O)2-, -S(O)N(RB)-, -

S(O)2N(RB)-, -C(O)N(RB)C(O)- -N(RB)C(O)N(RB')- - N(RB)SO2N(RB')-, or - N(RB)S(O)N(RB')-;

A and B are each independently C3-C12carbocycle or 3- to 12-membered heterocycle, and are each independently optionally substituted with one or more RA;

D is C3-C12carbocycle or 3- to 12-membered heterocycle, and is optionally substituted with one or more RA; or D is hydrogen or RA;

Y is selected from -T'-C(R1R2)N(R5)-T-RD, -T'-C(R3R4)C(R6R7)-T-RD, -LK-T-RD, or - LK-E;

R1 and R2 are each independently Rc, and R5 is RB; or R1 is Rc, and R2 and R5, taken together with the atoms to which they are attached, form a 3- to 12-membered heterocycle which is optionally substituted with one or more RA; R3, R4, R6, and R7 are each independently Rc; or R3 and R6 are each independently Rc, and R4 and R7, taken together with the atoms to which they are attached, form a 3- to 12- membered carbocycle or heterocycle which is optionally substituted with one or more RA;

Z is selected from -T'-C(R8R9)N(R12)-T-RD, -T'-C(R10R11)C(R13R14)-T-RD, -LK-T-RD, or -LK-E;

R8 and R9 are each independently Rc, and R12 is RB; or R8 is Rc, and R9 and R12, taken together with the atoms to which they are attached, form a 3- to 12-membered heterocycle which is optionally substituted with one or more RA;

R10, Rn, R13, and R14 are each independently Rc; or R10 and R13 are each independently Rc, and Rn and R14, taken together with the atoms to which they are attached, form a 3- to 12-membered carbocycle or heterocycle which is optionally substituted with one or more RA;

T and T' are each independently selected at each occurrence from bond, -LS-, -LS-M-LS'-, or -LS-M-LS'-M'-LS"-, wherein M and M' are each independently selected at each occurrence from bond, -O-, -S-, -N(RB)- -C(O)-, -S(O)2-, -S(O)-, -OS(O)- - OS(O)2-, -S(O)2O-, -S(O)O-, -C(O)O-, -OC(O)-, -OC(O)O-, -C(O)N(RB)-, - N(RB)C(O)- -N(RB)C(O)O-, -OC(O)N(RB)-, -N(RB)S(O)-, -N(RB)S(O)2-, - S(O)N(RB)- -S(O)2N(RB)- -C(O)N(RB)C(O)- - N(RB)C(O)N(RB')-, N(RB)SO2N(RB')-, -N(RB)S(O)N(RB')-, C3-d2carbocycle or 3- to 12-membered heterocycle, and wherein said C3-C12carbocycle and 3- to 12-membered heterocycle are each independently optionally substituted at each occurrence with one or more RA;

Lk is independently selected at each occurrence from bond, -LS-N(RB)C(O)-LS'- or -LS-C(O)N(RB)-LS'-; or C1-C6alkylene, C2-C6alkenylene or C2-C6alkynylene, each of which is independently optionally substituted at each occurrence with one or more RL; or C3-C12carbocycle or 3- to 12-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more RA;

E is independently selected at each occurrence from C3-C12carbocycle or 3- to 12-membered heterocycle, and is independently optionally substituted at each occurrence with one or more RA;

RD is each independently selected at each occurrence from hydrogen or RAj

RA is independently selected at each occurrence from halogen, nitro, oxo, phosphonoxy, phosphono, thioxo, cyano, or -LS-RE, wherein two adjacent RA, taken together with the atoms to which they are attached and any atoms between the atoms to which they are attached, can optionally form carbocycle or heterocycle;

RB and RB' are each independently selected at each occurrence from hydrogen; or C1-C6alkyl, C2-C6alkenyl or C2-C6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino,

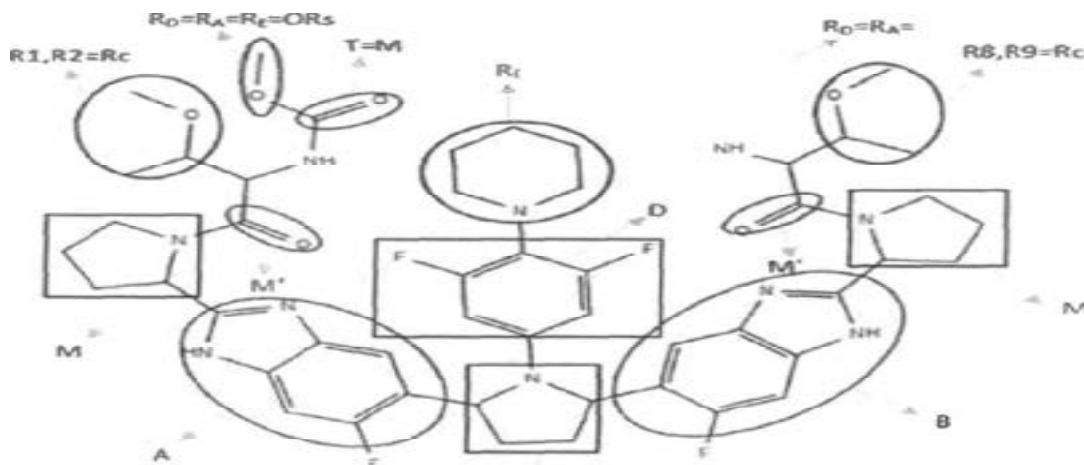
carboxy, nitro, oxo, phosphonoxy, phosphono, thioxy, formyl, cyano or 3- to 6- membered carbocycle or heterocycle; or 3- to 6-membered carbocycle or heterocycle; wherein each 3- to 6-membered carbocycle or heterocycle in RB or RB' is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxy, formyl, cyano, C1-C6alkyl, C2-C6alkenyl, C2-C6alkynyl, d-C6haloalkyl, C2-C6haloalkenyl or C2-C6haloalkynyl;

Rc is independently selected at each occurrence from hydrogen, halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxy, formyl or cyano; or C1- C6alkyl, C2-C6alkenyl or C2-C6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxy, formyl, cyano or 3- to 6-membered carbocycle or heterocycle; or 3- to 6-membered carbocycle or heterocycle; wherein each 3- to 6-membered carbocycle or heterocycle in Rc is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxy, formyl, cyano, C1-C6alkyl, C2-C6alkenyl, C2-C6alkynyl, C1- C6haloalkyl, d-C6haloalkenyl or C2-C6haloalkynyl;

RE is independently selected at each occurrence from -O-Rs, -S-Rs, -C(O)RS, -OC(O)RS, -C(O)ORS, -N(RSRS'), -S(O)RS, -SO2RS, -C(O)N(RSRS'), -N(RS)C(O)RS', -N(RS)C(O)N(RS'RS''), -N(RS)SO2RS', -SO2N(RSRS'), -N(RS)SO2N(RS'RS''), -N(RS)S(O)N(RS'RS''), -OS(O)-RS, -OS(O)2-RS, -S(O)2ORS, -S(O)ORS, -OC(O)ORS, -N(RS)C(O)ORS', -OC(O)N(RSRS'), -N(RS)S(O)-RS', -S(O)N(RSRS') or -C(O)N(RS)C(O)-RS'; or d-C6alkyl, C2-C6alkenyl or C2-C6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxy, formyl or cyano; or Cs-C6carbocycle or 3- to 6-membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxy, formyl, cyano, d-C6alkyl, C2-C6alkenyl, C2-C6alkynyl, C1-C6haloalkyl, C2-C6haloalkenyl or C2-C6haloalkynyl;

RL is independently selected at each occurrence from halogen, nitro, oxo, phosphonoxy, phosphono, thioxy, cyano, -O-RS, -S-RS, -C(O)RS, -OC(O)RS, -C(O)ORS, -N(RSRS'), -S(O)RS, -SO2RS, -C(O)N(RSRS') or -N(RS)C(O)RS'; or C3-C6carbocycle 3- to 6- membered heterocycle, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxy, formyl, cyano, C1-C6alkyl, C2-C6alkenyl, C2-C6alkynyl, C1-C6haloalkyl, d-C6haloalkenyl or d-C6haloalkynyl; LS, LS' and LS'' are each independently selected at each occurrence from bond; or C1- C6alkylene, C2-C6alkenylene or C2-C6alkynylene, each of which is independently optionally substituted at each occurrence with one or more RL; and RS, RS' and RS'' are each independently selected at each occurrence from hydrogen; C1- C6alkyl, C2-C6alkenyl or C2-C6alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxy, formyl, cyano or 3- to 6-membered carbocycle or heterocycle; or 3- to 6-membered carbocycle or heterocycle; wherein each 3- to 6-membered carbocycle or heterocycle in RS, RS' or RS'' is independently optionally substituted at each occurrence with one or more substituents selected from halogen, hydroxy, mercapto, amino, carboxy, nitro, oxo, phosphonoxy, phosphono, thioxy, formyl, cyano,

The above highlighted substituents can be deduced into the following structure:

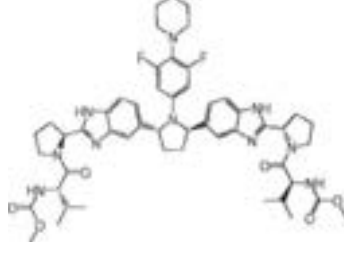
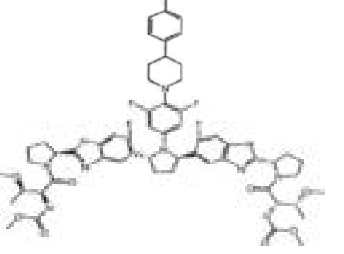
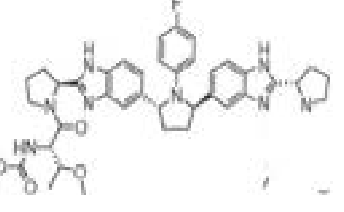
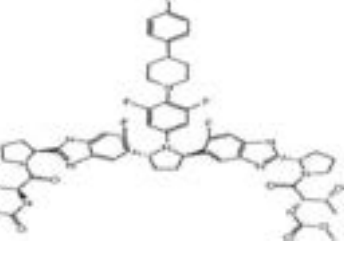


The substituent “D” in the ‘646 application includes only carbocyclic ring substituted with one or more RA (wherein two RA groups can form difluorophenyl ring and third RA can be LS –RE, in which Ls= a bond and RE = a 3-6 membered heterocycle= piperidine); this piperidine can be optionally substituted, but the substituents provided does not include the third ring of a halo substituted aryl group (a terminal 4-fluoro phenyl ring) (Refer to Pre-grant opposition para no.(iv) and (v) at PDF page no.18).

Therefore, the substitutions in the markush with Formula I of the impugned application ((Refer to page no.15 of the complete specification of the impugned application) stands disclosed in the

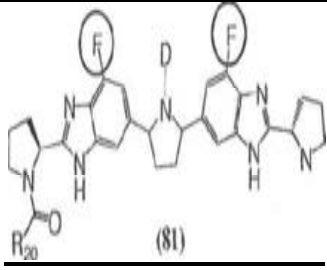
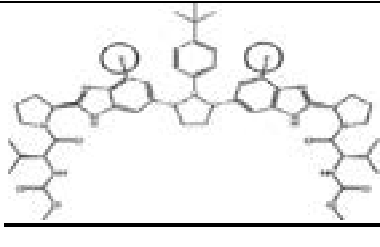
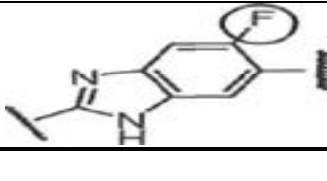
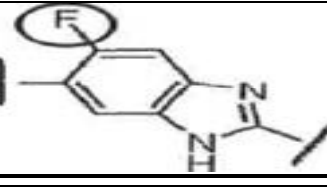
'646 application too. The '646 also exemplifies several compounds with structural similarities with claimed compound Pibrentasvir. The compound in example 271 share same core structure as that of Pibrentasvir. The compound of example 271 also has an EC50 value of less than 0.1nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS (Refer to line no.21 at page no.375 of the '646 specification @ Annexure part 2 PDF page no.751)

The table below exemplifies the overlapping similarities and differences between compounds disclosed in "646 and claimed compound Pibrentasvir.

WO/2010/144,646 (Annexure VIII)	Impugned Application
Example 271 Comprises valine in N-methoxycarbonyl amino acid chain. 	Example 3.52 (Pibrentasvir) includes substitution of the pyrrolidine extended with an additional fluorenyl moiety, the N-methoxycarbonyl amino acid chain comprises threonine instead of valine and benzimidazole ring substituted by fluorine atom. 
2nd last Compound at page no. 399 of the specification comprises N-methoxycarbonyl amino acid chain. (Refer to '646 specification at page no.399, pre-grant opposition annexure part 2 at PDF page no.775) 	

The opponents submit the combination of compounds exemplified in example 271 and 2nd last compound at page no.399 of the '646 specification can allow a person skilled in the art to experiment and arrive at the claimed compound Pibrentasvir.

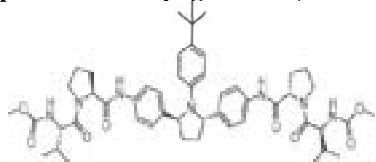
Even with the differences noted in halogen substitutions in the claimed compound, the disclosure of possible fluorine atom substitutions at benzimidazole ring in '646 application allows a person skilled in the art to undertake modifications of the central core of the structure. See for example the following compounds:

Compound 81, at internal page no.91. Refer to pre-grant opposition Annexure part 2 at PDF page no.467.	
Example 301 at page no.372. Refer to pre-grant opposition Annexure part 2 at PDF page no.748.	
Table 1a.A at page no.392. Refer to pre-grant opposition Annexure part 2 at PDF page no.768.	
Possible A rings Table 1b.B at page no.393. Refer to pre-grant opposition Annexure part 2 at PDF page no.769.	

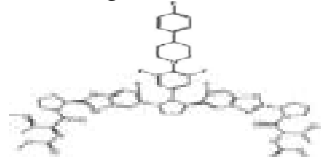
Therefore, the Opponents submit, that the selection of a fluoro-substituted benzimidazole is already known from the '646 application and a person skilled in the art would have been prompted to experiment with the compound of example 271 by adopting the fluorophenyl ring of 2nd last compound of page 399 in the central core of compound of example 271. Further, by adding a fluorine atom in each benzimidazole ring of compound of example 271, PSA would arrive at the claimed compound pibrentasvir. Thus, the claimed compound is obvious in light of the disclosures in the '646 application.

The '646 application also discloses another compound of example 35 (refer to specification internal page no.134 and PDF page no.510). Further the EC50 value of the compound was less than about 0.1nM in HCV 1b-Con1 replicon assays in the presence of 5% FBS (refer to specification internal page no.135 and PDF page no.511).

Example 35 (Ombitasvir) (Refer to '646 specification at internal page no.134 @ pre-grant opposition annexure part 2 at PDF page no.510)



Example 3.52 (Pibrentasvir) includes substitution of the pyrrolidine extended with an additional group, fluoro-substituted benzimidazole ring



instead of benzene linked to an amide and the N-methoxycarbonyl amino acid chain comprises threonine instead of valine.

The Opponents submit that the compound, Ombitasvir of example 35 serves as the starting point for further development of the claimed compound Pibrentasvir which also belongs to same class of drugs NS5A inhibitors and is also known to possess anti-HCV activity. A person skilled in the art would be motivated to experiment on the compounds disclosed in '646 application as it is well known in the pharmaceutical field to develop and optimize a drug they start from a known compound (compounds disclosed in '646), apply structural modifications, assess Structure Activity Relationship and thereafter analyze the pharmacokinetic and pharmacodynamic activities of the said drug. Therefore, the claimed compound Pibrentasvir is obvious as the central core structure and all the possible substitutions to the central core stands disclosed in the '646 application.

In particular modifications made to the compound Ombitasvir of Example 35, namely the replacement of the benzene linked to an amide by a benzimidazole ring, the addition of fluorine atoms on benzimidazole rings, the addition of further groups to the substituted pyrrolidine, and the replacement of the amino acid valine with threonine amino acid are obvious modifications when experimenting on discovering next generation NS5A inhibitors therefore claimed invention does not involve technical advance and lacks inventive step.

The Opponent referred to Annexure IX Wagner et al. (2018) J. Med. Chem. 61: 4052-4066 (Refer to pre-grant opposition @ Annexure part 3 PDF page no.1-15) and mentioned **though this is not a prior art document**, it is cited to emphasize that the **core structure of NS5A inhibitor in particular pyrrolidine stereochemistry design template comprising of an anchor, linker and end-cap was already available for the applicant**. This supports

our argument that compounds disclosed in '646 application serves as a **starting point** to discover the claimed compound. According to the inventors of this application they have admitted to have modified the anchor, linker and end-cap architecture of NS5A inhibitor design template to discover the next generation NS5A inhibitor Pibrentasvir which is the claimed compound. This is known prior to the claimed invention and a person skilled in the art can modify and substitute the structure therefore it is not inventive.

During the discovery of Pibrentasvir the possibility of considering other analog compounds disclosed in '646 application to interchange parts of these compounds with those of Ombitasvir is established. Therefore, selection of a threonine amino acid and a fluoro-substituted benzimidazole is already known from the '646 application and it is familiar choice to the person skilled in the art. Furthermore, the modification of the pyrrolidine core by combining the central

core of the compound of Example 271 and the second last compound of page no. 399 is also predictable choice which does not involve an inventive step.

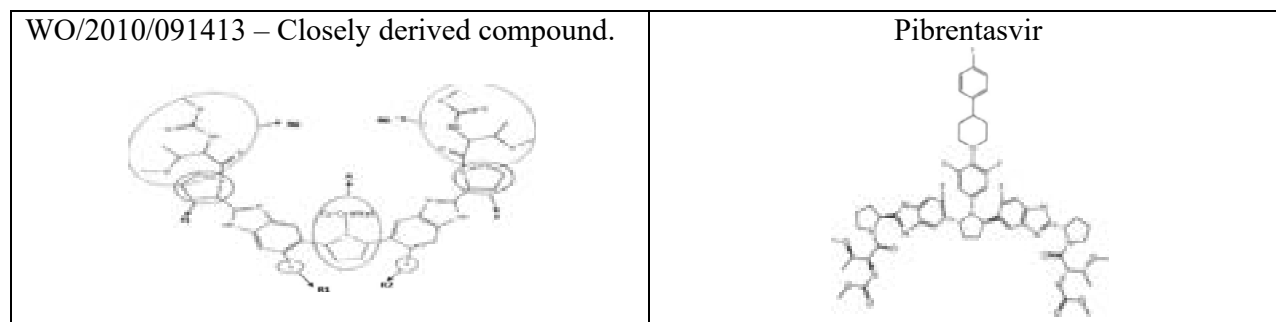
Therefore, a person skilled in the art would have been prompted to adapt the compound of Ombitasvir to experiment in replacing the amino acid, changing the central core structure and adding fluoro substituted benzimidazoles, thus arriving at Pibrentasvir. Therefore, the claimed compound Pibrentasvir does not involve an inventive step.

The Opponents refer to **Annexure X** WO/2010/091413 published on 12 August 2010 by Enanta Pharmaceuticals and it is before the earliest priority date of the impugned application 13 October 2010. (Refer to pre-grant opposition Annexure part 3 at PDF page no.16).

The '413 application relates to compounds which can inhibit the function of the NS5A protein encoded by HCV, its composition comprising these compounds, methods for inhibiting HCV viral replication, method for treating HCV infection and process of preparation of these compounds (see page 1 lines 5-9 of the specification). The compounds disclosed in this application also belongs to same class of inhibitors NS5A as seen in the impugned application.

The 413' teaches a compound of the following general structure wherein A can be a heterocyclic ring, wherein the heterocyclic ring can be pyrrolidinyl (see page 67 line 30, page 68 line 7 and claim 1) (Refer to pre-grant opposition at PDF page no. 25 to 29)

The structure when deduced with the possible substitutions leads to an overlapping structure with the general formula of the compounds of impugned application as shown in the below table. The compounds exhibit close structural resemblance with claimed compound with an anchor, linker and end-cap disclosed in the '413 application.

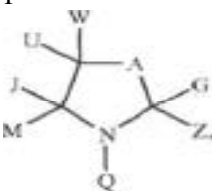
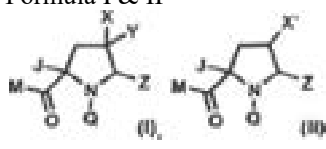
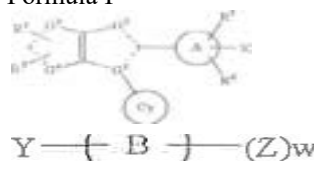
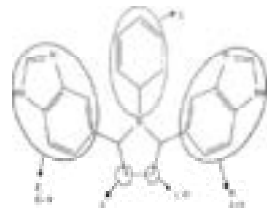
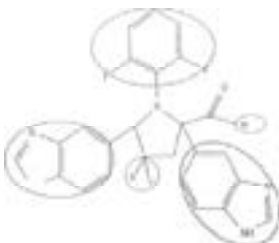
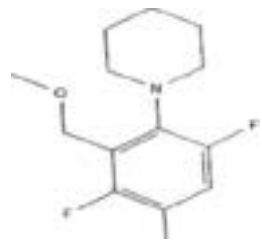


The Opponents submit that when '413 application compounds is compared with the claimed compound, firstly both of them are directed for use as DAA for use in the treatment of HCV infection, secondly except for the difference of presence of fluoro-substituted benzimidazole and presence of pyrrolidine ring in claimed compound both of them share same core structure thereby making it obvious and lacking any technical advance.

The opponent refers to **Annexure XI** US/2010/0074863 published on 25 March 2010, **Annexure XII** WO/2009/003009 published on 31 December 2008 and **Annexure XIII** US/2009/036444 published on 5 February 2009 to submit that all applications disclose compounds for use as anti-HCV agents. Further it also discloses compounds with **fused ring structure**, DAA compounds

having preference of **pyrrolidine at the core** and the possible **substitutions to pyrrolidine** is mentioned in the prior art documents. (Refer to pre-grant opposition at PDF page no. 31 to 39).

An in-depth analysis of these prior art documents informs a person skilled in the art about the possible disclosures of various anti-HCV DAAs and compounds disclosed serves as a starting point to arrive at the claimed compound, Pibrentasvir. Therefore, the alleged invention should be considered obvious in light of the prior art documents. The same is elucidated in the table below.

Annexure US/2010/0074863	XI	Annexure WO/2009/003009	XII	Annexure XIII US/2009/036444
Formula I 		Formula I & II 		Formula I 
Deduced from above markush 				
The substituents M and Z includes benzimidazole rings . Pyrrolidine at the core.		It teaches the “fixed” presence of a pyrrolidine core in HCV drugs.		It teaches pyrrolidine substitutions. Pyrrolidine ring attached to an aryl ring, which in turn is attached to a heterocyclic compound

APPLICANT SUBMISSION ON INVENTIVE STEP

Opponents case on Inventive step: With regard to inventive step, the Opponent relies on the following documents:

- (i) US2011/0207699: compound 3.42 in combination with compound 4.38;
- (ii) WO2010/144646: example 271, Markush structure and example 35 (Ombitasvir) and compound 81. The hypothetical structure created by the Opponent and relied as being the closest compound is

- M28T: Pibrentasvir is $\geq 7,500$ -fold more potent than Ombitasvir.

The EC₅₀ data confirms this — 1.5 pM for Pibrentasvir vs. 24,500 pM for Ombitasvir at the M28T mutation.

- Y93H: $\geq 1,500$ -fold improvement. Pibrentasvir EC₅₀ = 4.4 pM vs. Ombitasvir 113,000 pM.
- Y93C: ≥ 800 -fold improvement (1.2 pM vs. 4,570 pM).
- Q30E: ≥ 500 -fold improvement (1.69 pM vs. 3,620 pM).
- Q30R: ≥ 300 -fold improvement (1.2 pM vs. 2,180 pM).
- L31V: ≥ 130 -fold improvement (0.96 pM vs. 422 pM).

Across genotypes, Pibrentasvir is ≥ 50 -fold better against GT6a, ≥ 6 -fold better against GT1a, ≥ 3 -fold better against GT3a, and significantly better against GT2a, establishing pan-genotypic superiority.

(v) The additional data submitted shows the absolute replicon EC₅₀ values (pM) for Pibrentasvir alongside four prior art NS5A inhibitors namely Ombitasvir, Daclatasvir, Ledipasvir, and Elbasvir tested against wild-type GT1a and the panel of GT1a RASs observed in HCV patients treated with ombitasvir. Also, refer to para 21 of the written submission and article ‘Wong et al.’ Lower EC₅₀ values indicate greater antiviral potency. The colour coding reflects activity: green (potent/low EC₅₀), yellow (moderate), red (substantially impaired activity).

Replicon EC₅₀ (pM) - NS5A Inhibitor Comparison against GT1a Wild-Type and Resistance Variants

Compound WT GT1a Variants found in HCV patients treated with ombitasvir

M28T M28V Q30E Q30R L31V Y93C Y93H Y93N

pibrentasvir 0.78 1.5 1.3 1.69 1.2 0.96 1.2 4.4 5.1

ombitasvir 2.7 **24,500** 159 **3,620** **2,180** 422 **4,570** **113,000** **187,000**

daclatasvir 8.9 **1,860** 12 **77,900** 698 **5,440** **2,480** **24,700** **64,700**

ledipasvir 51 **1801** 78 **44000** **12,420** — **48,720** **86,430** **>500,000**

elbasvir 7 108 9 — 114 431 78 **1,543** **6,552**

(vi) Pibrentasvir Retains Near-Wild-Type Potency Across All Tested RASs:

The EC₅₀ data is compelling, surprising and unexpected. Pibrentasvir's EC₅₀ values across wild-type and all eight resistant variant to genotype 1a tested remain in a remarkably narrow and uniformly low range, between 0.78 pM (WT) and 5.1 pM (Y93N).

- Ombitasvir: EC₅₀ rises from 2.7 pM (WT) to 24,500 pM at M28T and 187,000 pM at Y93N: a loss of activity exceeding 69,000-fold at Y93N.
- Daclatasvir: EC₅₀ rises to 77,900 pM at Q30E and 64,700 pM at Y93N : a dramatic resistance.
- Ledipasvir: EC₅₀ exceeds 500,000 pM at Y93N : effectively no activity against this clinically prevalent variant.
- Elbasvir: EC₅₀ rises to 6,552 pM at Y93N and 1,543 pM at Y93H, representing meaningful resistance, though less severe than the other comparators.

By contrast, Pibrentasvir's highest EC₅₀ across all tested positions is 5.1 pM (Y93N): lower than the wild-type EC₅₀ of Ledipasvir (51 pM) and Elbasvir (7 pM).

The above results demonstrate that Pibrentasvir is a second-generation NS5A inhibitor with surprising, unexpected, non-obvious, and unpredictable advantages over prior-art NS5A inhibitors, including Ombitasvir, Daclatasvir, Ledipasvir, and Elbasvir. These structurally

distinct comparators could not have led a person skilled in the art to predict Pibrentasvir's superior activity. The results were not obtained through routine experimentation and are properly characterized as surprising and unexpected in view of the prior art. Accordingly, the claimed invention satisfies the inventive-step requirement under Section 2(1)(ja) of the Patents Act, 1970, because it demonstrates both (i) a clear and substantial technical advance over the state of the art and (ii) results that a person skilled in the art would not have achieved without inventive ingenuity.

Governing Legal Principles on Inventive Step / Obviousness

The Applicant at the hearing relied upon four case law for obviousness assessment.

The Applicant also relies on the following cases to demonstrate that there was a clear **teaching away / counterintuitive** in the prior art documents referred to by the Opponent and as discussed by the Applicant in the patent specification to arrive at the claimed compound or make any changes to any of the prior art compounds.

The Opponent has failed at each and every step of the five-step test for assessment of obviousness as laid down by the Hon'ble Division Bench of the Delhi High Court in *F. Hoffmann-La Roche Ltd v Cipla Ltd* and affirmed as the gold standard by the Division Bench in *Tapas Chatterjee v Assistant Controller of Patents and Designs* (2025:DHC:8824-DB).

The inventive concept is: a symmetric dimer NS5A inhibitor possessing a specific stereochemical configuration with specific moieties not found in any prior art, resulting in the molecule as a whole displaying superior and unexpected antiviral activity against HCV, including multiple genotypes and resistance-associated variants. No prior art individually or collectively teaches or suggests this combination.

A hypothetical compound constructed by mosaicking fragments from multiple documents cannot constitute a lead compound. The law is settled: only a real compound with demonstrated useful properties may serve as a lead compound (*BMS v BDR*, *Merck v Glenmark*). Each prior art document must be assessed based on its actual teaching, not on selective extraction of fragments to arrive at the target structure.

Each of the differences identified by the Opponent taken individually and cumulatively requires multiple theoretical and practical steps that a PSITA would not have taken without foreknowledge of the target structure. The substitution of threonine for valine, the introduction of fluorine on benzimidazole, and the selection of a specific pyrrolidine-aryl-arylheterocycloalkyl motif are not routine modifications suggested by any single document or combination. The overall molecular architecture of pibrentasvir a symmetric dimer with defined stereochemistry is not found in any prior art and represents a non-obvious structural choice whose significance could not have been predicted.

The technical advancement is **substantial, unexpected and clearly established**: Pibrentasvir's EC₅₀ values remain in the range of 0.78–5.1 pM across wild-type and all 8 tested NS5A RAS positions while all prior art NS5A inhibitors (Ombitasvir, Daclatasvir, Ledipasvir, Elbasvir) show dramatic loss of potency at these same positions, with EC₅₀ values reaching up to 187,000 pM (Ombitasvir/Y93N) and >500,000 pM (Ledipasvir/Y93N). These results are characterized in the specification as 'surprising and unexpected' and are objectively so no PSITA could have predicted, from any prior art combination, that the specific molecular architecture of Pibrentasvir

would achieve this profile. Conclusion: **The Opponent's obviousness case fails at every step of the Roche five-step test. The claimed compound is not obvious.**

SUBMISSIONS ON INDIVIDUAL PRIOR ART DOCUMENTS

Priority Date and Non-Prior Art Documents

The priority date of the present application is 13 October 2010, being the filing date of US12/903,822, in which Pibrentasvir (Example 3.52) is fairly disclosed. The Opponent's reliance on 25 February 2011 or 12 October 2011 as the priority date is legally incorrect and is liable to be rejected.

The following documents cited by the Opponent post-date the priority date and cannot constitute prior art under the Patents Act, 1970 for inventive step analysis:

US2011/0207699 is not prior art as it was published on 25 August 2011, after the priority dates of US12/903,822 (13 October 2010), US12/964,027, US61/446,800, and US13/100,827. **No submissions in relation to these documents should be taken on record.**

WO2010/144646 was published on 16 December 2010, after the priority date of 13 October 2010. The present application is entitled to claim priority from US'822 (13 October 2010), in which Pibrentasvir is disclosed, as discussed at para 46 of the present submissions. **WO'646 accordingly cannot be cited against the present application.**

Wagner et al. is from the same inventors and the same Applicant as the present application. It constitutes **post-filing data from the same inventive team** and does not constitute independent prior art.

WO2010/144646A2 (WO'646): Not Prior Art; No Motivation

WO2010/144646 is not prior art (published 16 December 2010, after priority date).

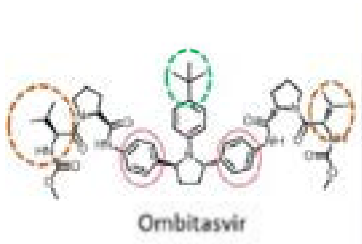
The submissions below are made without prejudice to and assuming without admitting that WO'646 is treated as relevant.

A hypothetical structure relied upon by the Opponent at page 17 of the Opposition Statement cannot constitute the closest prior art compound.

The law is unambiguous: a hypothetical structure assembled from Markush structures cannot serve as a lead compound.

Even relying on Example 271 and Example 35 (Ombitasvir) of WO'646, a PSITA would not arrive at pibrentasvir:

- No rationale was provided for selecting Example 271. It appears in a laundry list of compounds with $EC_{50} < 0.1$ nM without any basis for preferring it over hundreds of other exemplified compounds.
- The 5th compound on page 399 was randomly selected to fill structural gaps in Example 271, a textbook example of hindsight-driven cherry-picking.
- No reason was provided for introducing fluorine on the benzimidazole ring, a structural feature that requires specific design rationale.
- This is notwithstanding the fact that the chemical structure of Ombitasvir and the claimed compound Pibrentasvir are distinct in several respects from each other.

Ombitasvir (ABT-267) (e.g. example 37 of US568)	Pibrentasvir (ABT-530)
Published in Example 37 in US2010/0317568 dated 16th December 2010	Priority Date from US12/903,822 dated 13th October 2010 ~ Example 3.52 in 1310/DELNP/2013
	
Structural Differences	
Tert butyl methyl	(4-fluorophenyl)piperidin-1-yl]phenyl
Phenyl	benzimidazole-5-yl
Isopropyl	3-methoxy-1-oxobutan-2-yl carbamate

WO2010091413 (WO'413) — Hindsight Reconstruction

WO'413 discloses linked benzimidazole derivatives as NS5A inhibitors, with a Markush structure encompassing over 1,000 compounds (372 of Formula I, 357 of Formula II, 337 of Formula III) across Tables 1–23.

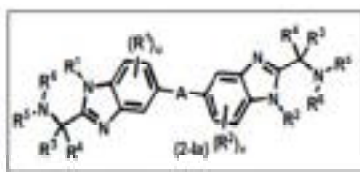
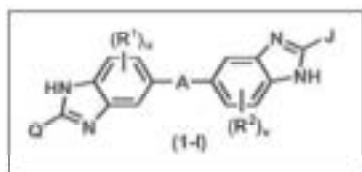


Table 25: Genotype-1b replicon EC₅₀

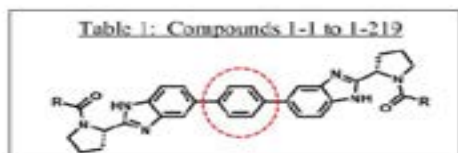
Principal Invention	Example	Range	Principal Invention	Example	Range	Principal Invention	Example	Range
First	1-2	C	First	1-3	C	First	1-20	C
First	1-25	A	First	1-26	A	First	1-42	A
First	1-52	A	First	1-54	A	First	1-62	C
First	1-67	C	First	1-70	C	First	1-72	C
First	1-78	C	First	1-83	C	First	1-114	C
First	1-354	C	First	1-357	A	First	1-361	A
First	1-362	C	First	1-364	C	First	1-366	C
First	1-367	C	First	1-368	A	First	1-369	C
First	1-370	C	First	1-371	C	First	1-372	C
Second	2-3a	C	Second	2-310	C	Second	2-354	C
Second	3-355	C	Second	2-357	A	Third	3-336	C
Third	3-337	C						

A >10 nM; B 1-10 nM; C <1 nM

The best compounds of WO '413 contains 'phenyl', 'pyrazine', 'biphenyl' or acyclic aliphatic or a urea group. (highlighted in document)

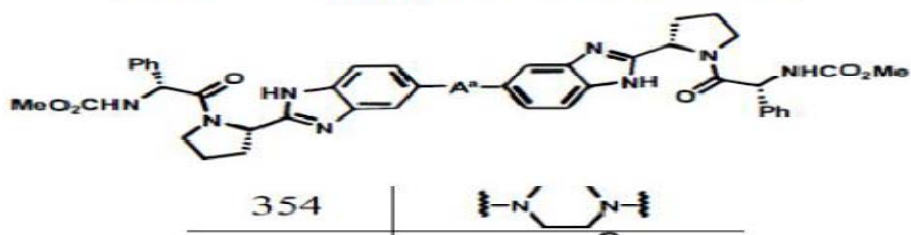
POSA from the teachings of WO'413 would derive any compounds of formula 1,2 and 3 comprising benzimidazole linker with A moiety selected from 'phenyl', 'pyrazine', 'biphenyl' or acyclic aliphatic.

Even if, one considers the compound having best activity, i.e., category 'C', EC₅₀ (HCV 1b) less than 1nM, there is no direction to modify the compounds in a manner to arrive at the claimed compound pibrentasvir.



2-354	
2-355	
2-357	
3-336	
3-337	

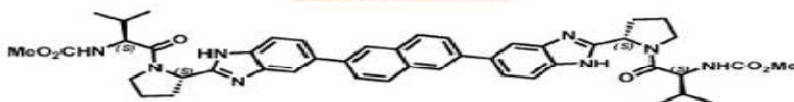
Table 8: Examples 1-310 to 1-360.



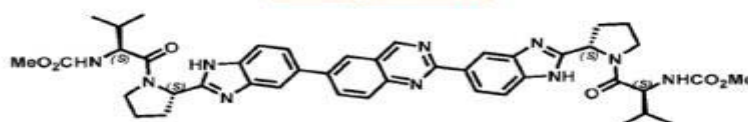
Example 1-362.



Example 1-364.

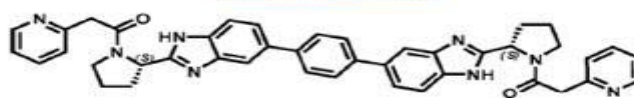


Example 1-366.



ound was synthesized from the compound from Example 365 u
nilar to that described in step 2b and Example 83. ESIMS m/z =

Example 1-367.



The Opponent's approach is flawed on the following grounds:

- **No motivation to select benzimidazole linker alone:** The document's teaching is to retain the dibenzimidazole as a linker not to take only one benzimidazole component and graft it onto an entirely different molecular framework.
- **Ignored the molecule as a whole:** The Opponent extracted a single structural feature (benzimidazole) while disregarding the overall molecular architecture that WO'413 teaches as being responsible for activity.
- **No direction for modification:** Even among the compounds with best activity (Category C, $EC_{50} < 1$ nM in HCV 1b replicon), WO'413 provides no direction to modify them in a manner that would lead toward Pibrentasvir.

- **Hindsight construction:** The hypothetical structure of Pibrentasvir was deduced from the Markush structure only after knowledge of the target molecule — this is precisely the approach condemned in *Merck v Glenmark* (para 100, 113).

US2010/0074863 (US'863): Non-Analogous Art; No Motivation

US'863 relates to pyrrolidine derivatives as anti-infective agents. It discloses 16 examples, none of which contains a benzimidazole side chain or a phenyl ring attached to the nitrogen of the pyrrolidine ring. The Q group in all examples consistently is 4-tert-butyl-3-methoxybenzoyl.

US'863 is a **non-analogous art reference**: the activity data reported therein relates exclusively to NS5B polymerase inhibition, not NS5A inhibition. NS5A and NS5B are distinct viral proteins functioning through completely different mechanisms (NS5A: phosphoprotein; NS5B: RNA-dependent RNA polymerase). A PSITA working on NS5A inhibitor design would have no motivation to consult a document that targets NS5B, addresses a different biological problem, and reports no NS5A activity data whatsoever.

Pharmacyclics LLC vs. Union of India (OA/46/2020/PT/DEL — MANU/IC/0044/2020) | Paras 16.18 & 18.3 (enclosed)

"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 invention. 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."

Titan Industries Ltd. vs. Controller of Patents (C.A.(COMM.IPD-PAT) 114/2022—2023:DHC:3832) | Para 9 — Hon'ble Justice Sanjiv Narula (enclosed)

While assessing lack of inventive step, the Court held that if two prior art documents address different problems, it would not be plausible for a PSITA to realistically combine their teachings. The Court further held that combining/mosaicking two substantially unrelated prior art references in order to invalidate a claim is inappropriate.

Kuraray Co. Ltd. & Ors. vs. Union of India (2023:MHC:5222) | Para 16 —Hon'ble Justice Senthilkumar Ramamoorthy (enclosed)

"As discussed above, the invention disclosed in prior art document D1 is intended to resolve a different problem and the said prior art teaches the use of a laminate for such purpose. Consequently, a person skilled in such prior art would not be motivated to consider the use of a PVA film on a standalone basis for resolving the problem that the claimed invention is targeted to resolve."

The Opponent's use of US'863 for mosaicking is therefore impermissible on the additional ground that it is a non-analogous art reference addressing a different technical problem (NS5B inhibition), a different viral target, and disclosing no activity relevant to NS5A inhibition.

The specific flaws in the Opponent's analysis of US'863 are:

- **Teaching of the document ignored:** The major teaching of US'863 is to retain the pyrrolidine core together with Q = 4-tert-butyl-3-methoxybenzoyl and Z = 1,3-thiazolyl to maintain activity. The Opponent has done the opposite —discarding these groups to construct a hypothetical compound.

- **Benzimidazole side chain:** No example in US'863 has a benzimidazole side chain. The Opponent's selection of benzimidazole from a laundry list of heteroaryl substituents was driven solely by hindsight knowledge of Pibrentasvir.
- **Non-obvious substitutions:** Even assuming the pyrrolidine core from US'863, a PSITA would not: (i) substitute Q = benzene and further difluorobenzene with a 4-fluorophenyl-piperidin-1-yl; (ii) select benzimidazole as Z from a lengthy list of heterocycles; (iii) add fluorine to benzimidazole; or (iv) introduce a threonine moiety — none of which are taught or suggested.

WO'009: Non-Analogous Art (NS5B Inhibitor)

WO'009 discloses substituted pyrrolidine compounds as HCV inhibitors of NS5B (RNA-dependent RNA polymerase). WO'009 is a **non-analogous art reference**: it targets a completely different protein (NS5B) through a distinct mechanism, addresses a different technical problem, and discloses no NS5A activity data.

A PSITA with expertise in NS5A inhibitor design would have no motivation to consult WO'009, which addresses NS5B inhibition, a different problem requiring different design principles.

- The document discloses 500+ compounds across seven principal inventions (pages 134–253). The consistent teaching is Q = 4-tert-butyl-3-methoxybenzoyl; Z = 1,3-thiazol-2-yl or related heterocycles. No benzimidazole linker is present.

- The Opponent's hypothetical construction selecting Q = substituted aryl and Z = benzimidazole directly contradicts the teaching of the document and is purely hindsight driven.

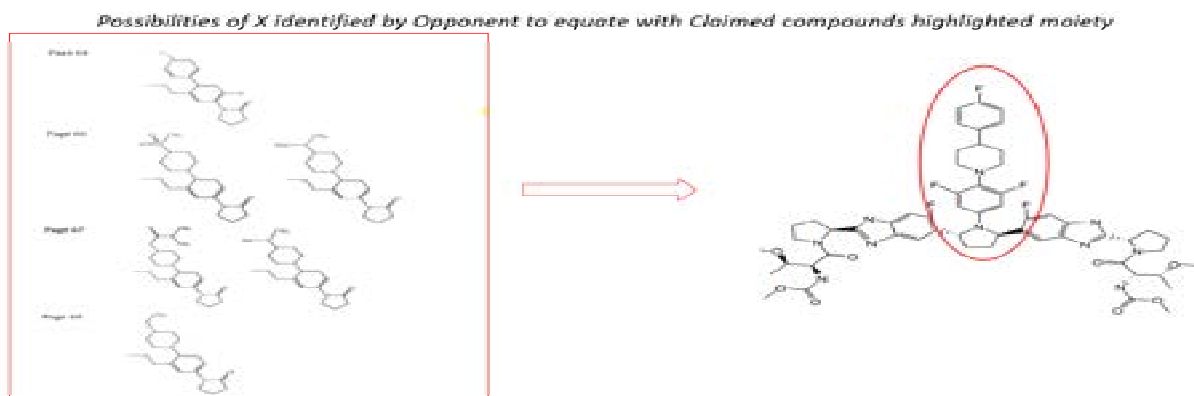
- The Opponent has acknowledged that groups C(=O)M and X, Y (or X') are elements of difference when compared to the core of the claimed compounds yet provides no motivation for bridging these differences.

The non-analogous art case law cited at Section B.4 above applies with equal force to WO'009.

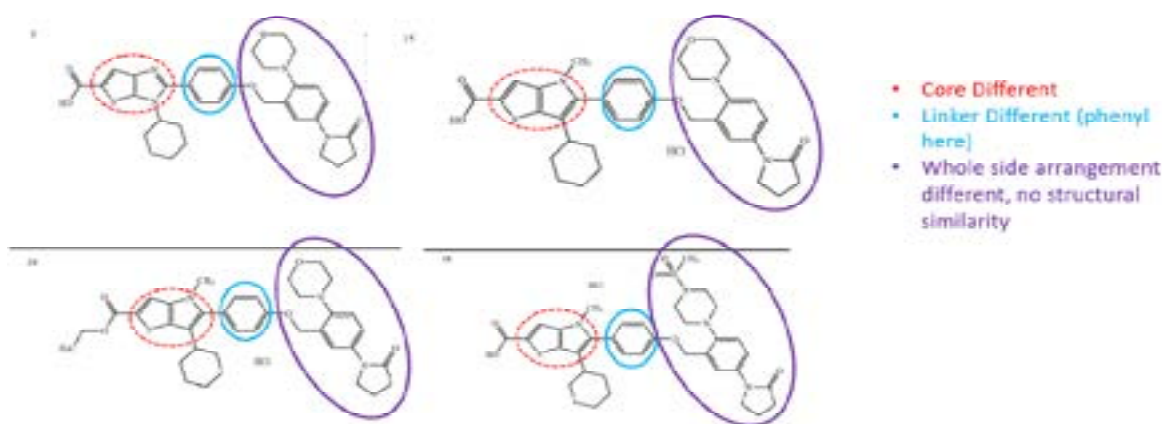
US2009/0036444 (US'444) ≈ WO2005/049622A1: Irrelevant Core; No Rational Selection

US'444 relates to 5-5-membered fused heterocyclic compounds as HCV polymerase inhibitors. The Opponent relies on the side chain of selected compounds to map against the central core of Pibrentasvir a fundamentally flawed approach.

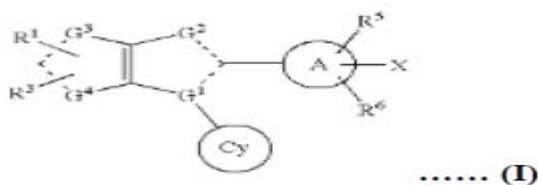
Opponent has merely in a desperate attempt considered the side chain for mapping with the central core of pibrentasvir having pyrrolidine attached to aryl ring and further attached to aryl ring through heterocycloalkyl linker



As identified by the opponent itself from their representation, Table 18, Page 116 of the document, the compounds possessing highest activity are 5, 15, 18 and 24



US'444 is related to 5-5-membered fused heterocyclic compound of formula (I) and use thereof as HCV polymerase inhibitor.

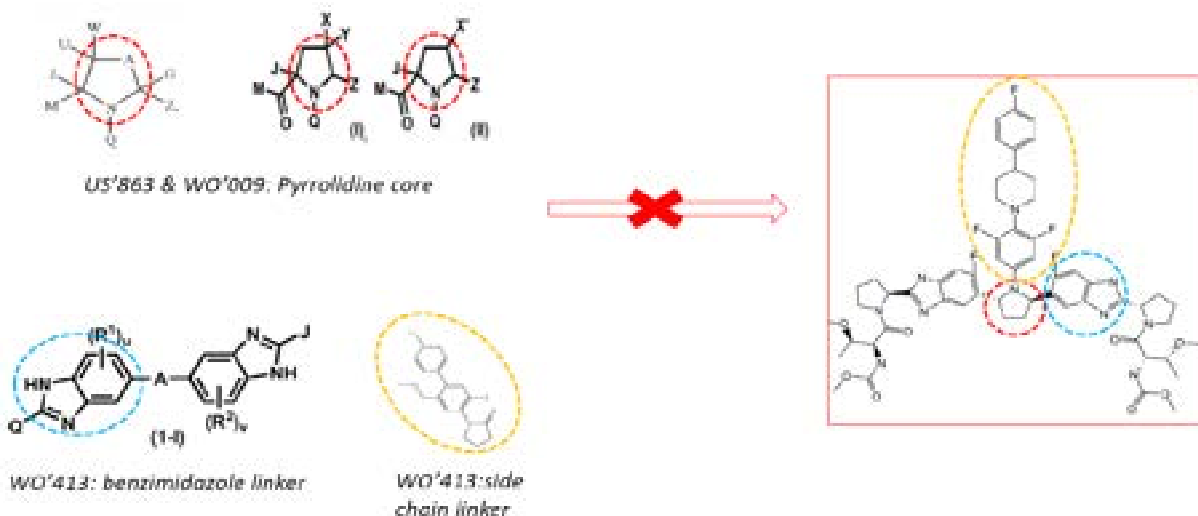


The 5-5-membered fused heterocyclic core of US'444 which is the defining structural feature of that document has been entirely disregarded by the Opponent. Ignoring the core while extracting only a side chain is impermissible under settled law (BMS v BDR, principle (iv)).

The side chain in US'444 contains a pyrrolidinone ring not a pyrrolidine ring as in Pibrentasvir. The aryl ring is attached to the 5-5-membered core through a benzoyl linker not through the pyrrolidine-aryl-aryl-heterocycloalkyl motif of Pibrentasvir.

The compounds with highest activity in US'444 (Table 18, page 116: compounds 5, 15, 18, 24) which are the correct starting point for any PSITA do not suggest the structural modifications required to arrive at Pibrentasvir.

The Opponent's argument to combine WO'413 with US'863 & WO'009 is a flawed approach. The Opponent's reliance on Annexures X–XIII to mosaic WO'413 + US'863 + WO'009 + US'444 requires a level of hindsight that is unacceptable. Each selection decision is guided by foreknowledge of Pibrentasvir not by the teachings of the prior art.



Structural Distinction: Pibrentasvir vs. Ombitasvir (also refer to para 52 above)

Notwithstanding the Opponent's reliance on ombitasvir (Example 35/37) as a reference point, pibrentasvir and ombitasvir are structurally distinct in several key respects, as set out below:

Ombitasvir (ABT-267) Example 37 of US2010/0317568 Published: 16th December 2010	Pibrentasvir (ABT-530) Example 3.52 of 1310/DELNP/2013 Priority Date: 13th October 2010
Structural Feature	Structural Feature
tert-Butyl methyl	(4-Fluorophenyl)piperidin-1-yl]phenyl
Phenyl	Benzimidazol-5-yl
Isopropyl	3-Methoxy-1-oxobutan-2-yl carbamate (Threonine-derived)

These differences are not cosmetic. As held by the Hon'ble Delhi High Court in *Merck v Glenmark* (para 105) (enclosed as previously said), the biological activity of a molecule is completely dependent on the structure as a whole — each part of the molecule makes a contribution to the overall biological effect. The substitution of a simple tert-butyl methyl group with the elaborate (4-fluorophenyl)piperidin-1-yl]phenyl moiety, and of a phenyl group with a fluorinated benzimidazole, represents a non-obvious structural departure whose pharmacological consequences could not have been predicted.

Molecule as a Whole: Biological Activity Determined by Overall Structure

Merck Sharp & Dohme Corporation vs. Glenmark Pharmaceuticals Ltd. (CS(OS) 586/2013 & CC No. 46/2013 — I.A. Nos. 9827/2013, 8048/2014 & 13626/2015) |
Para 105 — Hon'ble Justice A.K. Pathak (enclosed as previously said)

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.

The Opponent's fragmented analysis which extracts individual structural features from multiple documents and constructs a hypothetical mosaic fails to assess pibrentasvir's molecular architecture as a whole. The symmetric dimer structure, defined stereochemistry, fluorinated benzimidazole moieties, and specific amino acid chain all contribute to the biological profile that the Opponent has failed to predict or explain.

Conclusion: The Opponent's pre-grant opposition must be dismissed in its entirety. The claimed compound Pibrentasvir (Example 3.52) is novel, inventive, and industrially applicable. The Opponent has failed at every step of the Roche five-step obviousness test; has relied on four documents that are not prior art; has constructed a hindsight-driven mosaic of hypothetical structures in lieu of demonstrating that a PSITA would arrive at the claimed invention; has cited non analogous art (US'863 targeting NS5B; WO'009 targeting NS5B) without basis; and has failed entirely to engage with the extraordinary technical advancement demonstrated by Pibrentasvir over all prior art NS5A inhibitors.

OPPONENTS SUBMISSION

Amended Claim 1 is not patentable under Section 25(1)(f) under Section 3(d)

The Opponents submit the applicant has not shown any specific detailed data of the claimed compound, Pibrentasvir in the specification which shows an advance over and above the compounds disclosed in the prior art documents. Further, post facto data submitted by applicant cannot be considered.

The data mentioned in Page no.81, 406 and 407 of the impugned complete specification includes data for compounds of Example 3.48, **3.52**, 4.38 and 5.1 and all of them have same HCV activity. It is unclear as to why specifically compound of example 3.52 (Pibrenstasvir) alone was chosen out of these four compounds. Specific detailed experimental data pertaining to claimed compound of Example 3.52 is not provided in the complete specification.

The applicant argument on secondary considerations that impugned application is already granted patent in other countries should be disregarded. Patent law is territorial in nature and standards of patentability varies across countries there is no persuasive value for grant of patent in India. The applicant is obligated to fulfill the requirements of patentability as mandated under Indian patent law.

The Opponents conclude that the claimed compound is obvious in light of prior art documents, a person skilled in the art would be motivated to arrive at Pibrentasvir and it lacks inventive step and it also fails to satisfy the requirements of Section 3(d).

APPLICANT SUBMISSION

NON-PATENTABILITY UNDER SECTION 25(1)(f)

The Opponent's objection under Section 25(1)(f) is rejected. The specification discloses substantial biological activity data establishing the superior anti-HCV activity of the claimed compound.

The Applicants respectfully submit that the pending claim 1 does not fall within the purview of Section 3(d) of the Patents Act.

a) Pibrentasvir is a new chemical entity

The Applicants respectfully submit that the pending claim relates to a new chemical entity, i.e., Pibrentasvir, that was NOT known at the priority date and not a new form of known substance.

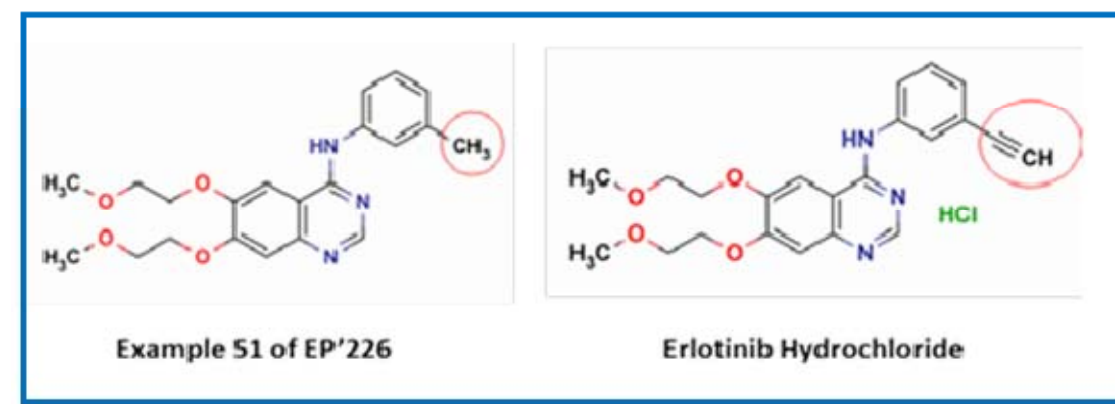
The Applicants further submit that requirement of providing comparative activity data under Section 3(d) of the Patent Act, 1970, arises only once it is established that the compounds of the patent application are salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of a known substance. The claimed compounds of the present invention relate to a new chemical entity, and therefore, Section 3(d) does not apply.

The Applicants submit that the law regarding section 3(d) is very clear. If a substance is known, it should have known efficacy for the requirement under Section 3(d) of the Patents Act, 1970. 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.

A chemical derivative, in the broader scientific sense, often results in the creation of a new molecule altered physicochemical properties, and distinct biological activity. Such a molecule cannot be said to retain the identity of the parent compound and, therefore, falls outside the ambit of Section 3(d). To interpret “derivative” in Section 3(d) otherwise so broadly as to include all chemically related compounds would lead to a manifest absurdity, namely, that any new chemical entity could be denied patent protection merely because it can be retrospectively traced to a known scaffold. This would effectively collapse the statutory distinction between novelty and inventive step on the one hand, and Section 3(d) on the other, rendering the patent regime unworkable.

This position is consistent with the law laid down by the Hon’ble Supreme Court in *Novartis AG v. Union of India*, where it was categorically held that Section 3(d) is a carefully calibrated provision intended to prevent evergreening by disallowing trivial modifications of known substances, and not to bar patentability of genuine inventions involving new chemical entities. The Court emphasized that the provision applies only where the claimed invention is a “new form of a known substance,” which presupposes the continued identity of the underlying substance.

In this regard reference is made on the decision of the *Division Bench of the Hon’ble Delhi High Court in Roche vs Cipla* that clearly held that Erlotinib is an NCE with respect to Example 51 of EP’226 (prior art) as shown below. The court clearly held that section 3(d) is not applicable.



Further, the term ‘derivative’ used in the explanation part of Section 3(d) should not be confused with the term ‘derivative used in the context of organic chemistry’. The ‘derivative compounds as used in the organic chemistry’ are different chemical compounds and are thus different substances.

The Applicant submits that in organic chemistry, a derivative is defined as a compound that is derived from a similar compound by a chemical reaction. A derivative is produced by formation of a covalent bond between the compound being derivatized and a group provided by a chemical reagent when a reaction is performed between the compound and a chemical reagent. Some form of other energy source such as heat or light could also represent a chemical reagent. A derivative generally consists of the same skeleton or core chemical structure such as core ring structure and cannot deviate too far away from the original starting compound. Sometimes a literal definition is not applied for derivatives particularly when written in title to represent a very large group of molecules listed in a patent or in a publication. It is merely used for simplification of writing to avoid writing names of each compound individually.

The Applicant submits that the expression ‘derivative’ used in section 3(d) has to be given a meaning such that it falls within the same category as ‘salt, ester, ether, polymorph, metabolite, pure form, particle size, isomer, mixture of isomers, complex or combination’. This is in accordance with the legal principle of ‘ejusdem generis’, the literal translation of which is ‘of the same kind’ and which in the interpretation of statutes implies that where a law lists specific classes of persons or things and then refers to them in general, the general statements only apply to the same kind of persons or things specifically listed. The concept of ‘ejusdem generis’ which is a latin expression and commonly used while interpreting statutes.

b) Comparative Data:

Arguendo and even though Section 3(d) is not applicable, the Applicants have provided comparative data in the patent specification. The specification discloses substantial biological activity data establishing the superior anti-HCV activity of the claimed compound.

The specification (page 81, first paragraph) discloses EC_{50} values for Examples 3.48, 3.52 (Pibrentasvir), 4.38, and 5.1, compared against Example 37 of US2010/0317568 (Ombitasvir). The following unexpected advantages are disclosed:

- ≥ 6 -fold lower EC_{50} against HCV Genotype 1a
- ≥ 3 -fold lower EC_{50} against HCV Genotype 3a

- ≥ 50-fold lower EC₅₀ against HCV Genotype 6a
- Significantly lower EC₅₀ against HCV Genotype 2a
- ≥ 130-fold lower against L31V variant
- ≥ 7,500-fold lower against M28T variant
- ≥ 80-fold lower against M28V variant
- ≥ 500-fold lower against Q30E variant
- ≥ 300-fold lower against Q30R variant
- ≥ 800-fold lower against Y93C variant
- ≥ 1,500-fold lower against Y93H variant
- Significantly lower against Q30H variant

This data constitutes direct experimental evidence of superior anti-HCV activity and satisfies any requirement for disclosure of biological activity.

The requirement to provide comparative efficacy data under Section 3(d) of the Patents Act, 1970 arises only where the claimed compound is a salt, ester, ether, polymorph, metabolite, pure form, particle size, isomer, mixture of isomers, complex, combination, or other derivative of a known substance.

Furthermore, the novel and inventive compound, Pibrentasvir, of the impugned application is marketed as a commercial product Mavyret® (Pibrentasvir in combination with Glecapravir) has been granted regulatory approval in approximately 60+ countries, which itself shows enhanced efficacy. Pibrentasvir, of the impugned application is marketed as a commercial product Mavyret® (Pibrentasvir in combination with Glecapravir) is the only regulatorily approved treatment option for patients with either acute or chronic HCV and has cured more than one million patients worldwide.

In this regard, the Applicants have referred to the order of BMS Vs BDR, DHC, CS(COMM) 27/2020, para 45 (enclosed as previously said)

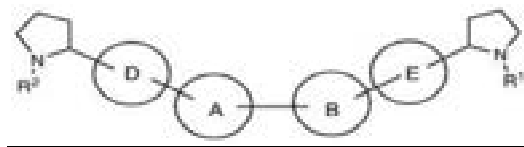
Para 45

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 aforesaid, the Applicant submits that Pibrentasvir is a new chemical entity (NCE) and therefore, Section 3(d) is not attracted.

APPLICANT'S SUBMISSION ON OBJECTIONS IN HEARING NOTICE

Document D1 discloses compound of formula (I) treatment of HCV infection

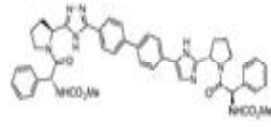
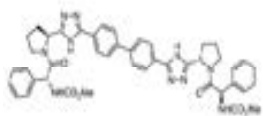
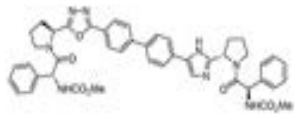
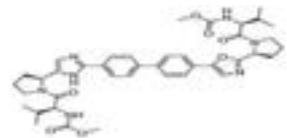


wherein *A* and *B* are each phenyl;

D and *E* are each five-membered aromatic rings containing one, two, or three heteroatoms independently selected from nitrogen, oxygen, and sulfur; provided that at least one of *D* and *E* is other than imidazole;

*R*₁ and *R*₂ are independently selected from hydrogen, *R*₃-C(O)-; and each *R*₃ is independently selected from alkoxy, alkoxyalkyl, alkoxy carbonyl, alkoxy carbonyl alkyl, alkyl, alkyl carbonyl alkyl, aryl, aryl alkyl, aryl alkoxy, aryl alkyl, aryloxy alkyl, cycloalkyl, (cycloalkyl) alkyl, (cycloalkyl) alkyl, cycloalkyloxy alkyl, haloalkyl, heterocyclyl, heterocyclyl alkyl, heterocyclyl alkoxy, heterocyclyl alkyl, heterocycliloxy alkyl, hydroxy alkyl, -NRcRd, (NRcRd) alkyl, (NRcRd) alkyl, and (NRcRd) carbonyl.

The structure of compounds disclosed in D1, WO' 380, are as follow:

Example -3 	Example -33 
Example 34 	Example 36 
Example 37 	

It is clearly evident from the structures exemplified in D1 and Markush formula of D1 that the compound of present invention belongs to different class of compounds and are irrelevant for novelty and inventive step analysis of compound of the present invention. The same is explained below in detail:

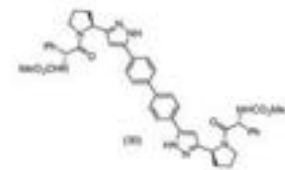
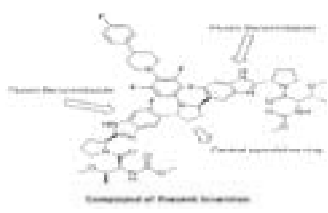
The core structure as well the arrangement of various groups and rings in the present invention and compounds of D1 are entirely different. The compound of the present invention consists of central **pyrrolidine** ring (tri-substituted) substituted with 2,5-bis fluoro benzimidazole ring and 4-(4-fluorophenyl)-piperidin-1-yl-phenyl residue in position 1 of the pyrrolidine. However, the compounds disclosed in D1 consist of central **biphenyl ring** di-substituted further with two rings namely di-pyrazole, pyrazole and triazole, di-triazole, pyrazole and oxazole etc.

Further the moiety **3-methoxy 1-oxo butan-2yl carbamate** attached to pyrrolidine ring in the compound of the present invention is also very different with respect to compounds of D1. The structurally unrelated compounds do not provide any motivation to person skilled in art to arrive at compounds of present invention.

In view of the above two differences, Table 4 of WO2012/051361 shows that by inserting a pyrrolidinyl between the biphenyl (e.g., BMS-790052), the antiviral activity of the modified

compound significantly improves against HCV genotype 1a (i.e., 1200 vs ≥ 10000 , in the presence of 40% HP or human plasma), although there is a significant drop in activity for genotype 1b (e.g., 2400 vs 60, in the presence of 40% HP or human plasma). Please note that lower EC50 means greater antiviral activity.

A direct comparison of our compound to daclatasvir shows that the compound of the present invention has significantly improved activities against all HCV genotypes. Please note that EC50 of the compound of the present invention in Table 4 were determined in the presence of 5% fetal bovine serum; but BMS-790052 (i.e., daclatasvir) in Table 1 were determined in the absence of 5% fetal bovine serum. As a result, if fetal bovine serum was added to the daclatasvir assays, its EC50 would be even higher (i.e., antiviral activities would be even lower).

D1 WO2008/144380A1	Present Invention
 Example 30	 Compound of the present invention
a) The central moiety, biphenyl, has planar structure. b) Di-substituted biphenyl core. c) Contains heterocycles such as pyrazole, triazole, and oxazole. d) Lacks corresponding piperidinephenyl substitution.	a) The central moiety, pyrrolidine is linked to 2,5-bis-fluoro benzimidazole moieties, via a stereospecific bond, (R,R) configuration. b) Tri-substituted pyrrolidine core. c) Contains 2,5-bis-fluoro benzimidazole moieties. d) Incorporates 4-(4-fluorophenyl)-piperidin-1-yl-phenyl substituent.

For the compound of the present invention, there is a “D” group further added to the inserted pyrrolidinyl (the last compound in Table 5 of WO2012/051361). The antiviral activity of the compound of the present invention drastically improved over that without the “D” group. For genotype 1a, the EC50 (in the presence of 40% HP or human plasma) is 0.2; for genotype 1b, the EC50 is 0.1, both of which are multiple orders of magnitude lower than the compounds in Table 4.

The “D” group on the compound of the present invention actually interacts with a new binding site on the NS5A protein target. Daclatasvir does not have any moiety to interact with this new binding site, because daclatasvir is a linear structure and does not have a moiety that is about perpendicular to the linear backbone. See paragraphs [0122]-[0123] of US2011/0137633.

At the very outset, we submit that while applying the above principles laid down by the Court, POSA based on D1 would not have received any hint from the said documents to modify them so as to arrive at the claimed compound of the present invention.

(i) The prior art consistently teaches away from pibrentasvir’s structural features, demonstrating inventive choice.

(ii) **Biphenyl Linker (Table 1):** Daclatasvir employs a biphenyl linker between imidazole moieties. Table 1 shows that replacing this linker with alternatives significantly reduces anti-HCV activity. The teaching of the prior art was to retain the biphenyl linker. Pibrentasvir departs from this teaching, and does not include biphenyl linker between imidazole moieties which is demonstrating an inventive choice.

(iii) **Benzimidazole Substitution (Table 2):** Table 2 demonstrates that fluorine substituted benzimidazole compounds exhibit worse anti-HCV activity than unsubstituted benzimidazole. The prior art teaches away from the fluorine substituted benzimidazole present in pibrentasvir.

(iv) **Pyrrolidinyl Linker (Tables 3–4):** Table 3 shows that compounds with an unsubstituted pyrrolidinyl linker have substantially reduced anti-HCV activity. However, Table 4 reveals that substitution of the pyrrolidinyl nitrogen with a carbocycle or heterocycle dramatically improves activity.

I am not repeating the submissions of the applicants for the sake of brevity.

The results demonstrate that Pibrentasvir is a second-generation NS5A inhibitor with surprising, unexpected, non-obvious, and unpredictable advantages over prior-art NS5A inhibitors, including Ombitasvir, Daclatasvir, Ledipasvir, and Elbasvir. These structurally distinct comparators could not have led a person skilled in the art to predict Pibrentasvir's superior activity.

The results were not obtained through routine experimentation and are properly characterized as surprising and unexpected in view of the prior art. Accordingly, the claimed invention satisfies the inventive-step requirement under Section 2(1)(ja) of the Patents Act, 1970, because it demonstrates both (i) a clear and substantial technical advance over the state of the art and (ii) results that a person skilled in the art would not have achieved without inventive ingenuity. In view of the aforementioned, the Applicant submits that the claimed compound, Pibrentasvir, is novel and inventive.

After going through the submission of the applicant as regard to inventive step objection, the claimed invention does not lack novelty and inventive step in light of the teachings of the cited document D1, either alone or in combination. The amended claims are inventive over the cited document. I am not repeating the submissions of the applicant for the sake of brevity.

Regarding objection under section 3(d), the revised claim 1 does not fall within the purview of Section 3(d) of the Patents Act, as it relates to a new chemical entity, i.e., Pibrentasvir, that was not known at the priority date and not a new form of known substance. I am not repeating the submissions of the applicants for the sake of brevity.

OPINION OF THE CONTROLLER ON THE VARIOUS GROUNDS OF OPPOSITION:

The following is the analysis and observation of the Controller on the various grounds of opposition:

At the hearing on 16/06/2026, the opponents did not press the grounds of opposition under Section 25(1)(a) and Section 25(1)(i). The opponent has focused on grounds of opposition under sections 25(1)(e) and 25(1)(f). No arguments were made by the opponents at the hearing as to

why the Applicant was not entitled to the priority date of October 13, 2010, based on US2012/903822 in view of Section 11 of the Indian Patents Act.

GROUND I: Entitlement to Earliest Priority Date

The Applicant contends that Claim 1 is entitled to the earliest priority date of 13 October 2010, being the filing date of US12/903,822, on the ground that pibrentasvir (Example 3.52) is "fairly based" on the matter disclosed in priority document. Relying on the similarity between Section 11 of the Act and Section 5(2) of the UK Patents Act, 1949. The Applicant relies on T.A. Blanco-White and applied in Mond Nickel Co.'s Application and Letraset Ltd. v. Rexel Ltd., namely it may fairly be assumed that for priority claiming at that is required is that the priority document may describe the invention in general rather than specific terms, and the Applicant is not required to define the scope of the invention at that stage.

The applicant claims priority from US12/903,822 dated 13 October 2010. It submits that Pibrentasvir is fairly disclosed and enabled by the Markush disclosure and general method of preparation said to be contained in that priority application. The Applicant has also provided a feature mapping in which it identifies pyrrolidine; L1/L2 bond; benzimidazole; proline + threonine; L3 bond; and difluoro-substituted piperidine further substituted by 4-fluorophenyl as corresponding to disclosures which it attributes to US12/903,822, including Example 6.11 and Scheme XXIV. The applicant consequently submits that the present Claim 1 is "fairly based" upon the earlier priority application. The Applicant asserts that US12/903,822 also contains a general method of preparation applicable to the relevant compounds.

The Opponent submits that US12/903,822 and US12/964,027 contain only a Markush structure, a general method of preparation and a possible list of multiple NS5A compounds and do not explicitly disclose Pibrentasvir/Example 3.52. According to the Opponent, the specific compound was first disclosed in US61/446,800 dated 25 February 2011, and that date should therefore be treated as the effective priority date.

Analysis and findings on Priority

The Applicant has placed a specific structural mapping in hearing. That mapping is not contradicted by an identified passage from the underlying priority document. The Opponent's submission that the earlier document contains only a Markush genus is therefore a substantive contention. Likewise, the Applicant's assertion that Example 6.11 and Scheme XXIV support the claimed combination is a submission which cannot, in the absence of the underlying document.

The Opponent has not identified, in its written submission, a particular essential structural integer of Claim 1 which it demonstrates to be wholly absent from US12/903,822. Its objection principally rests upon the proposition that the earlier disclosure is broad and does not expressly identify Pibrentasvir.

Having considered the Applicant's structural mapping and its reliance upon Example 6.11 and Scheme XXIV the relevant structural features forming the claimed compound are within the scope of and the Applicant has established on basis the present record the subject matter of

Claim 1 as fairly based upon US12/903,822. Accordingly the effective priority date of Claim 1 is 13 October 2010. The Opponent's objection to the priority date is therefore rejected.

GROUND II: LACK OF INVENTIVE STEP [Section 25(1)(e)] read with section 2(1)(ja))

In consequence of the finding in above paragraph, the status of each cited document is determined as follows:

Document	Publication Date
US2011/0207699	25 August 2011 (Not prior art)
WO2010/144646	16 December 2010 (Not prior art)
Wagner et al. (2018)	13 April 2018 (Not prior art)
US2010/0267634	21 October 2010 (Not prior art)
WO2010/091413	12 August 2010 (Prior art)
US2010/0074863	25 March 2010 (Prior art)
WO2009/003009	31 December 2008 (Prior art)
US2009/036444	5 February 2009 (Prior art)

WO2010/144646 (WO'646).

The document WO'646 discloses a broad Markush genus (Formula I) and Example 35 (Ombitasvir), Example 271, and further, a compound at page 399. The Opponents' case is that a PSITA, starting from Example 271 or from Ombitasvir (Example 35), would be prompted to graft a fluorophenyl-substituted moiety from the compound at page 399 onto the core of Example 271/Ombitasvir, and separately to add fluorine atoms to the benzimidazole rings a modification said to be already disclosed, in generic terms, within WO'646's own substituent definitions thereby arriving at pibrentasvir.

Ombitasvir (Example 35/37) and pibrentasvir are structurally distinct in more than one material respect the tert-butyl methyl group of Ombitasvir is replaced in pibrentasvir by a (4-fluorophenyl)piperidin-1-yl]phenyl moiety, the phenyl ring is replaced by a benzimidazol-5-yl ring, and the isopropyl-based carbamate is replaced by a threonine-derived 3-methoxy-1-oxobutan-2-yl carbamate. These are not trivial or cosmetic substitutions in a molecule whose biological activity, on the well-established medicinal-chemistry principle relied upon in Merck

Sharp & Dohme Corp. v. Glenmark Pharmaceuticals Ltd. (para 105), depends on the contribution of each part of the structure to the whole.

The Opponents have not shown that WO'646 provides any teaching or motivation to select Example 271 (out of a very large number of exemplified compounds) as a starting point in preference to any other as the Applicant submits, hindsight-driven, it is only knowledge of the target molecule, pibrentasvir, that renders this particular combination (out of the many mathematically possible combinations within the genus) apparent. For these reasons, WO'646, does not establish obviousness of Claim 1.

WO2010/091413 (WO'413), US2010/0074863 (US'863), WO2009/003009 (WO'009), and US2009/0036444 (US'444).

These four documents are considered together because the Opponents' case in respect of each follows a similar pattern, a Markush genus is identified, a hypothetical structure is constructed by selecting particular substituents said to correspond to features of pibrentasvir, and it is then asserted that the resulting hypothetical structure demonstrates "close structural resemblance" sufficient to render the claim obvious.

The Opponents have not identified in respect of any of these four documents, a specific exemplified compound possessing useful anti-HCV NS5A activity that a PSITA would independently have selected as a starting point. Nor they have established any rational chain of modification leading from any such a compound to pibrentasvir.

Both documents US'863 and WO'009 are directed to inhibition of a different, non-analogous viral target whereas pibrentasvir and the claimed invention concern inhibition of the HCV NS5A protein. US'863 and WO'009 are concerned with NS5B, the RNA-dependent RNA polymerase, a mechanistically and structurally distinct enzyme. It is reflected in the decisions relied by the Applicant that a reference addressing a different technical problem, through a different mechanism, is not analogous art and a PSITA engaged in NS5A inhibitor design would have no particular reason to consult NS5B-directed literature in preference to the substantial NS5A-specific literature (including WO'646). As regards US'444, which the Opponents' own submissions describe as relating to a 5-5-membered fused heterocyclic core with anti-HCV polymerase activity. The Opponents rely only on a side-chain feature abstracted from selected compounds, while disregarding the defining bicyclic core of that document an approach again inconsistent with the requirement, principle that a compound must be assessed as a whole and not by selective extraction of a fragment convenient to the case sought to be made.

For these reasons, none of WO'413, US'863, WO'009 or US'444, whether taken singly or in combination establishes that the claimed compound would have been obvious to the PSITA.

The complete specification discloses, at pages 81 and 406–408, comparative EC50 (replicon) data for pibrentasvir against Ombitasvir across HCV genotypes 1a, 2a, 3a and 6a and against a panel of clinically observed NS5A resistance-associated substitutions. This data records improvements ranging from approximately 3-fold (genotype 3a) to in excess of 7,500-fold (variant M28T). Further additional data relied upon by the Applicant with reference to third-party literature situates pibrentasvir's with high barrier resistance compared to Ombitasvir, Daclatasvir, Ledipasvir and Elbasvir as well. A technical improvement of this order of magnitude, particularly at resistance-conferring mutation positions rather than merely against wild-type virus, is not the kind of result that would ordinarily be expected from the routine substituent modifications.

Analysis and findings

Claim 1 is an NS5A inhibitor and the claimed subject matter is a specific molecular architecture involving a symmetric/dimeric arrangement, defined stereochemistry, fluorinated benzimidazole components, a particular pyrrolidine arrangement, a threonine-containing side chain, and a substituted piperidine/fluorophenyl structure.

The relevant prior arts do not provide a single clear route to Claim 1. WO2010/091413 provides NS5A background but does not disclose or sufficiently motivate the complete claimed combination. The earlier documents US2010/0074863, WO2009/003009 and US2009/036444 are relied upon primarily for general HCV/NS5A chemistry and pyrrolidine/substitution concepts. The Opponent has not demonstrated why the skilled person would combine those disclosures in the precise manner necessary to arrive at Pibrentasvir which is the type of hindsight reconstruction.

The Opponent's case relies upon taking different structural components from different documents and combining them. The Applicant characterises this as a hindsight-driven mosaic. The Applicant specifically identifies substitution of threonine for valine, fluorination of benzimidazole and selection of the particular pyrrolidine/aryl architecture as requiring multiple steps not suggested by any single prior-art reference. The Opponent has not demonstrated a coherent pre-priority-date pathway that would lead the skilled person to those combined selections.

The Applicant relies upon experimental data showing superior antiviral activity and resistance characteristics. The Applicant identifies at least six-fold lower EC50 against HCV genotype 1a, at least three-fold lower EC50 against genotype 3a, at least fifty-fold lower EC50 against genotype 6a, and substantial improvements against various resistance-associated variants. The Applicant further submits that Pibrentasvir demonstrates EC50 values in the picomolar range across wild-type and resistance-associated variants.

The Applicant characterizes the inventive concept as a specific stereochemically defined NS5A inhibitor exhibiting a superior antiviral and resistance profile. The inventive concept of Claim 1 is a dimeric NS5A inhibitor compound bearing a defined stereochemical configuration,

fluorinated benzimidazole rings on both arms, and an N-methoxycarbonyl-O-methyl-L-threonyl substituent, which in combination genotypic anti-HCV activity together with a higher resistance barrier against clinically significant NS5A resistance-associated substitutions (RASs), as compared to first-generation NS5A inhibitors including Ombitasvir, Daclatasvir, Ledipasvir, and Elbasvir.

Therefore the Opponent has not established that Claim 1 would have been obvious to the person skilled in the art. The objection under Section 25(1)(e) is rejected.

GROUND III — NON-PATENTABILITY UNDER SECTION 25(1)(f) READ WITH SECTION 3(d)

The Applicant submits that Pibrentasvir is a new chemical entity. None of the documents relied upon by the Opponents discloses Pibrentasvir itself, whether as a specifically identified substance or in the form of a salt, ester, polymorph, or any other recognised derivative of an identified prior compound. Indeed, the Opponents' own case considered that Pibrentasvir is a structurally distinct compound rendered obvious by combination of teachings from several documents. Such a case in the nature of an inventive-step objection, and cannot be as an objection under Section 3(d) directed to a disclosed derivative of a known substance.

Applying the reasoning in *F. Hoffmann-La Roche Ltd. v. Cipla Ltd.* (as relied upon by the Applicant with reference to erlotinib), that Section 3(d) is not attracted as a matter of Claim 1. The Opponents contend that the specification does not adequately distinguish, by data, why Example 3.52 was selected as the claimed compound in particular to Examples 3.48, 4.38 or 5.1, each showed comparable activity.

Arguendo and even though Section 3(d) is not applicable, the Applicant has provided comparative data in the patent specification. The specification discloses substantial biological activity data establishing the superior anti-HCV activity of the claimed compound. The specification (page 81, first paragraph) discloses EC₅₀ values for Examples 3.48, 3.52 (Pibrentasvir), 4.38, and 5.1, compared against Example 37 of US2010/0317568 (Ombitasvir). The comparative EC₅₀ data showing the superiority of pibrentasvir over Ombitasvir across genotypes and resistance variants appears at pages 81 and 406–408 of the complete specification.

As to why Example 3.52 rather than Examples 3.48, 4.38 or 5.1 was selected for the claim, it is well settled that an applicant is entitled to claim a particular species falling within a broader disclosure to justify that selection over other disclosed species, provided the selected species itself meets the requirements of novelty, inventive step and sufficiency each of which has been examined above and found to be satisfied in respect of Example 3.52/pibrentasvir specifically, by reference to data specific to that compound. The ground of opposition under Section 25(1)(f) read with Section 3(d) accordingly rejected.

Analysis and findings

The Applicant submits that Pibrentasvir is a new chemical entity and is not merely a new form of a known substance and therefore Section 3(d) is not attracted. Further, the Applicant submits the comparative EC50 data showing the superiority of pibrentasvir over Ombitasvir across genotypes and resistance variants appears at pages 81 and 406–408 of the complete specification.

The Opponent has not established that Pibrentasvir is merely a salt, ester, ether, polymorph, metabolite, isomer, combination or other form of a known substance having the statutory relationship contemplated by Section 3(d). Mere structural resemblance to previously disclosed NS5A inhibitors is insufficient. Thus, the Pibrentasvir constitutes a new chemical entity for the purpose of Section 3(d).

The Opponent relies on Section 25(1)(f) read with Section 3(d). However, the Opponent's written submissions merely establish a structural comparison with known NS5A inhibitors and do not demonstrate that Pibrentasvir constitutes a new form of a previously known substance within the meaning of Section 3(d). A structural relationship or a common therapeutic target, in itself, is insufficient to establish the statutory relationship under Section 3(d). Accordingly, the objection under Section 3(d) is not established. Thus, the objection under Section 25(1)(f) read with Section 3(d) is rejected.

CONCLUSION

After careful consideration of the written submissions of the Opponents and the Applicant, the amended claim is found to be novel and involve an inventive step over the prior-art documents cited by the Opponents. The Opponents have not been able to substantiate the grounds raised under Sections 25(1)(a), 25(1)(i), 25(1)(e) and 25(1)(f) of the Patents Act, 1970. Accordingly, the said grounds of opposition are dismissed.

Having considered all the facts and submissions made by the Applicant's agent during the hearing and in the written submission as well as in view of all the documents on record, the objections raised u/s 25(1) by the opponents, are considered as complied and the Pre-grant opposition under section 25(1) of the Patents Act filed against the application number 1310/DELNP/2013 is dismissed and I hereby proceed for grant of the instant application with 1 claim as filed by the applicant on 30/06/2026.

Dated: 28/09/2026

Dr. Archana Gupta
(Deputy Controller of Patents and Designs)