FORM 7A
THE PATENTS ACT,
1970 (39 OF 1970)
AND
THE PATENTS RULES, 2003
REPRESENTATION FOR OPPOSITION TO GRANT OF PATENT
[See Rule 55]

We, **LOW COST STANDARD THERAPEUTICS,** an Indian Company of I Floor, Premananda Sahitya Bhavan, Opposite Lakadipul, Dandia Bazar, Vadodara, 390 001, Gujarat, India, hereby give representation by way of opposition to the grant of patent in respect of application No: **201817002543 filed on 22/01/2018** made by **ABBVIE INC.** on the grounds:

(a) Section 25(1)(b): Lack of novelty
(b) Section 25(1)(e): Lack of inventive step
(c) Section 25(1)(f): Invention is not patentable under section 3(d), 3(e) and 3 (i)
(d) Section 25(1)(g): The complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed.
(e) Section 25(1)(h): Failure to disclose the information required by section 8 of the Patents Act.

(Detailed grounds are set out in the Opposition as attached)

My address in India is:

RAJESHWARI & ASSOCIATES
S-357, FIRST FLOOR
NEAR HDFC BANK
PANCHSEEL PARK,
NEW DELHI-110017, INDIA
TEL +91-11-41038911
MOBILE NO: 9910206718

Dated this 28th day of December, 2022

RAJESHWARI H. IN/PA – 0358
OF RAJESHWARI AND ASSOCIATES
AGENT FOR THE OPPONENT

THE CONTROLLER OF PATENTS
THE PATENT OFFICE, NEW DELHI

BEFORE THE CONTROLER OF PATENTS, THE PATENT OFFICE, NEW DELHI

In the matter of Section 25(1) of The Patents Act, 1970 as amended by The Patents (Amendment) Act 2005;

And

In the matter of Rule 55 of The Patents Rules 2003 as amended by the Patent (Amendment) Rules, 2006

And

IN THE MATTER of Indian Patent Application 201817002543 filed on 22/01/2018 in the name of ABBVIE INC.

REPRESENTATION BY:

LOW COST STANDARD THERAPEUTICS **.....OPPONENT**

VS.

ABBVIE INC. **.....APPLICANT**

REPRESENTATION BY WAY OF PRE-GRANT OPPOSITION UNDER SECTION 25(1) OF THE PATENTS ACT, 1970

We, **LOW COST STANDARD THERAPEUTICS**, hereby submit my representation by way of opposition to the grant of patent in respect of Indian Patent Application 201817002543 dated 22/01/2018 in the name of ABBVIE INC. titled "Solid Pharmaceutical Compositions for Treating HCV".

STATEMENT OF CASE OF OPPONENT

1. The Opponent has learnt that the Applicant has filed an Indian Patent Application 201817002543 (hereinafter "the Impugned Patent Application") on 22/01/2018. The impugned patent application was published in the official journal of the patent office on 27/04/2018, which is currently pending before the Patent Office. The Impugned Patent

Application is the national phase application of PCT/US2016/039266 and draws its priority from US application 62/185,145 dated 26 June 2015, US application 62/186,154 dated 29 June 2015, US application 62/193,639 dated 17 July 2015 and US application 62/295,309 dated 15 Feb 2016.

2. The Impugned Patent Application is entitled "Solid Pharmaceutical Compositions For Treating HCV".

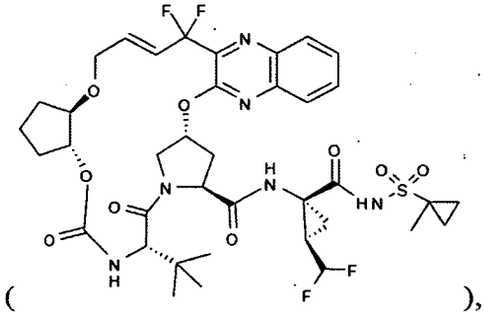
3. The Opponent by way of this present pre-grant opposition submits that the claims currently pending on record are not patentable under the provisions provided in this Act. The claims as filed and currently on record are annexed herewith as **Annexure-1** and reproduced herein below for ready reference:

1. A solid oral pharmaceutical dosage formulation comprising:

a first composition comprising:

50% to 80% by weight of one or more pharmaceutically acceptable polymers, and

100 mg Compound 1



( ),

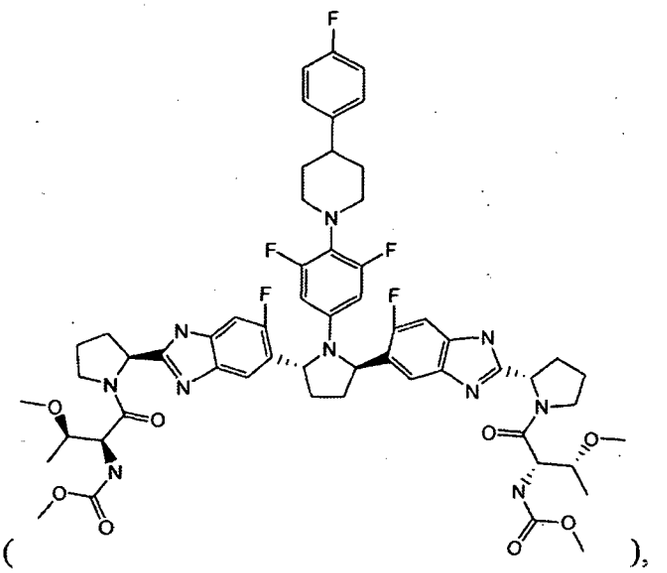
wherein the weight percentage of the one or more pharmaceutically acceptable

polymers is relative to the total weight of the first composition; and

a second composition comprising:

50% to 80% by weight of one or more pharmaceutically acceptable polymers, and

40 mg Compound 2



),

wherein the weight percentage of the one or more pharmaceutically acceptable polymers is relative to the total weight of the second composition;

wherein the formulation is a tablet comprising a first layer and a second layer, the first layer comprising the first composition and the second layer comprising the second composition; and

wherein administration of three of the tablets to a population of healthy, non-fasted adult humans results in a mean C_{max} value between about 333 ng/mL and about 1113 ng/mL for Compound 1.

2. The solid oral pharmaceutical dosage formulation as claimed in claim 1, wherein the first composition comprises a first amorphous solid dispersion comprising Compound 1.

3. The solid oral pharmaceutical dosage formulation as claimed in claim 1, wherein the second composition comprises a second amorphous solid dispersion comprising Compound 2.

4. The solid oral pharmaceutical dosage formulation as claimed in claim 2, wherein the first amorphous solid dispersion comprises the one or more pharmaceutically acceptable polymers.

5. The solid oral pharmaceutical dosage formulation as claimed in claim 2, wherein the first amorphous solid dispersion further comprises one or more pharmaceutically acceptable surfactants.

6. The solid oral pharmaceutical dosage formulation as claimed in claim 4, wherein the first amorphous solid dispersion further comprises one or more pharmaceutically acceptable

7. The solid oral pharmaceutical dosage formulation as claimed in claim 3, wherein the second amorphous solid dispersion comprises the one or more pharmaceutically acceptable polymers.

8. The solid oral pharmaceutical dosage formulation as claimed in claim 3, wherein the second amorphous solid dispersion further comprises one or more pharmaceutically acceptable surfactants.

9. The solid oral pharmaceutical dosage formulation as claimed in claim 7, wherein the second amorphous solid dispersion further comprises one or more pharmaceutically acceptable surfactants.

10. The solid oral pharmaceutical dosage formulation as claimed in claim 6, wherein the one or more pharmaceutically acceptable polymers comprise copovidone, and the one or more pharmaceutically acceptable surfactants comprise Vitamin E TPGS.

11. The solid oral pharmaceutical dosage formulation as claimed in claim 9, wherein the one or more pharmaceutically acceptable polymers comprise copovidone, and the one or more pharmaceutically acceptable surfactant comprises Vitamin E TPGS.

12. The solid oral pharmaceutical dosage formulation as claimed in claim 11, wherein the one or more pharmaceutically acceptable surfactants further comprise propylene glycol monocaprylate.

13. The solid oral pharmaceutical dosage formulation as claimed in claim 1, wherein

the first composition comprises a first amorphous solid dispersion comprising Compound 1, one or more pharmaceutically acceptable polymers and one or more pharmaceutically acceptable surfactants; and

the second composition comprises a second amorphous solid dispersion comprising Compound 2, one or more pharmaceutically acceptable polymers and one or more pharmaceutically acceptable surfactants.

14. The solid oral pharmaceutical dosage formulation as claimed in claim 13, wherein the one or more pharmaceutically acceptable polymers comprise copovidone, and the one or more pharmaceutically acceptable surfactants comprises Vitamin E TPGS.

15. The solid oral pharmaceutical dosage formulation as claimed in claim 3, wherein

the first amorphous solid dispersion comprises Compound 1, one or more pharmaceutically acceptable polymers comprising copovidone, and one or more pharmaceutically acceptable surfactants comprises Vitamin E TPGS; and

the second amorphous solid dispersion comprises Compound 2, one or more pharmaceutically acceptable polymers comprising copovidone, and one or more pharmaceutically acceptable surfactants comprising Vitamin E TPGS and Propylene glycol monocaprylate.

16. The solid oral pharmaceutical dosage formulation as claimed in claim 1, wherein the first amorphous solid dispersion comprises 10% to 40% by weight of Compound 1, and the second amorphous solid dispersion comprises 5% to 20% by weight of Compound 2.

17. The solid oral pharmaceutical dosage formulation as claimed in claim 1, wherein the first amorphous solid dispersion comprises 15% to 30% by weight of Compound 1, and the second amorphous solid dispersion comprises 5% to 15% by weight of Compound 2.

18. The solid oral pharmaceutical dosage formulation as claimed in claim 13, wherein the first amorphous solid dispersion comprises 15% to 30% by weight of Compound 1, and the second amorphous solid dispersion comprises 5% to 15% by weight of Compound 2.

19. The solid oral pharmaceutical dosage formulation as claimed in claim 15, wherein the first amorphous solid dispersion comprises 15% to 30% by weight of Compound 1, and the second amorphous solid dispersion comprises 5% to 15% by weight of Compound 2.

20. The solid oral pharmaceutical dosage formulation as claimed in claim 1, wherein the first layer further comprises a disintegrant.

21. The solid oral pharmaceutical dosage formulation as claimed in claim 20, wherein the disintegrant comprises Croscarmellose sodium.

22. The solid oral pharmaceutical dosage formulation as claimed in claim 1, wherein the first layer and the second layer further comprise a lubricant.

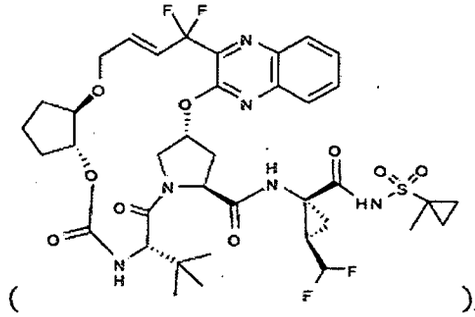
23. The solid oral pharmaceutical dosage formulation as claimed in claim 22, wherein the lubricant comprises sodium stearyl fumarate.

24. A solid oral pharmaceutical dosage formulation comprising:

a first composition comprising:

50% to 80% by weight of one or more pharmaceutically acceptable polymers, and

100 mg Compound 1



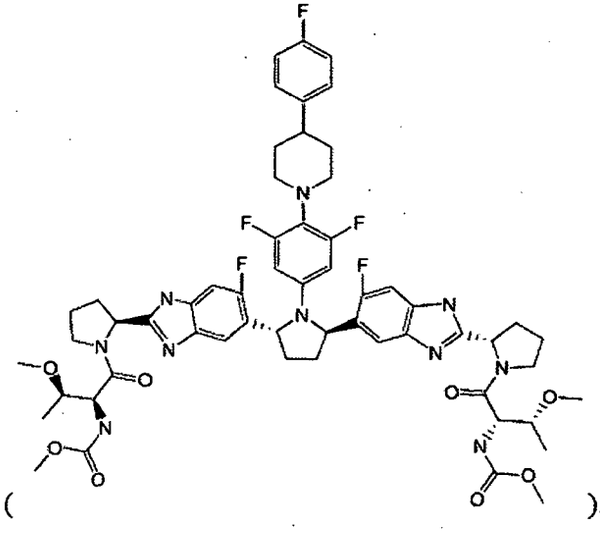
( ),

wherein the weight percentage of the one or more pharmaceutically acceptable polymers is relative to the total weight of the first composition; and

a second composition comprising:

50% to 80% by weight of one or more pharmaceutically acceptable polymers, and

40 mg Compound 2



( ),

wherein the weight percentage of the one or more pharmaceutically acceptable polymers is relative to the total weight of the second composition;

wherein the formulation is a tablet comprising a first layer and a second layer, the first layer comprising the first composition and the second layer comprising the second composition; and

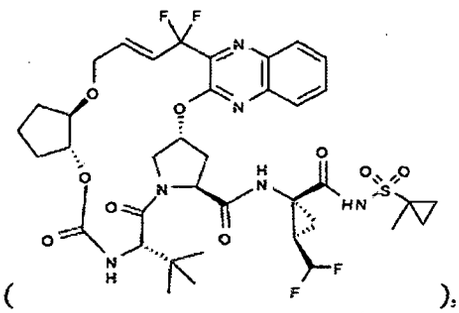
wherein administration of three of the tablets to a population of healthy, non-fasted adult humans results in a mean AUC value between about 1099 ng·h/mL and about 3680 ng/mL for Compound 1.

25. A solid oral pharmaceutical dosage formulation comprising:

a first composition comprising:

50% to 80% by weight of one or more pharmaceutically acceptable polymers, and

100 mg Compound 1



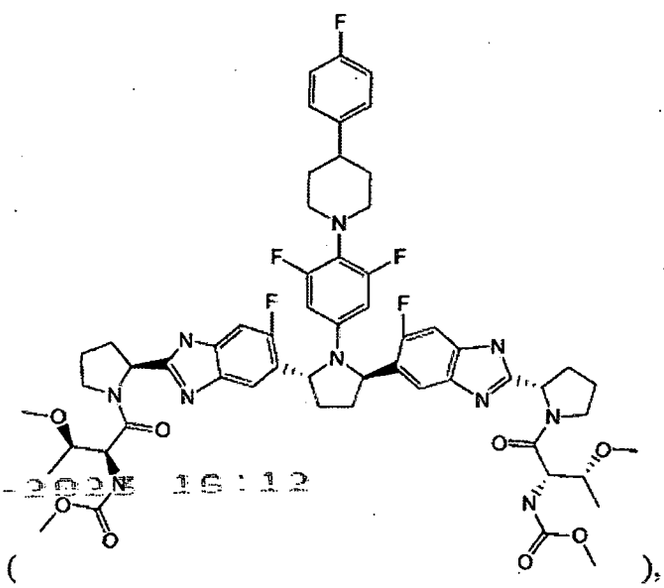
( ),

wherein the weight percentage of the one or more pharmaceutically acceptable polymers is relative to the total weight of the first composition; and

a second composition comprising:

50% to 80% by weight of one or more pharmaceutically acceptable polymers, and

40 mg Compound 2



( ),

wherein the weight percentage of the one or more pharmaceutically acceptable polymers is relative to the total weight of the second composition;

wherein the formulation is a tablet comprising a first layer and a second layer, the first layer comprising the first composition and the second layer comprising the second composition; and

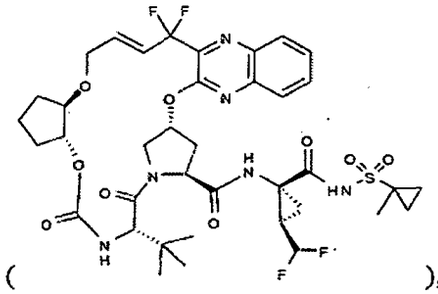
wherein administration of three of the tablets to a population of healthy, fasted adult humans results in a mean C_{max} value between about 85 ng/mL and about 684 ng/mL for Compound 1.

26. A solid oral pharmaceutical dosage formulation comprising:

a first composition comprising:

50% to 80% by weight of one or more pharmaceutically acceptable polymers, and

100 mg Compound 1



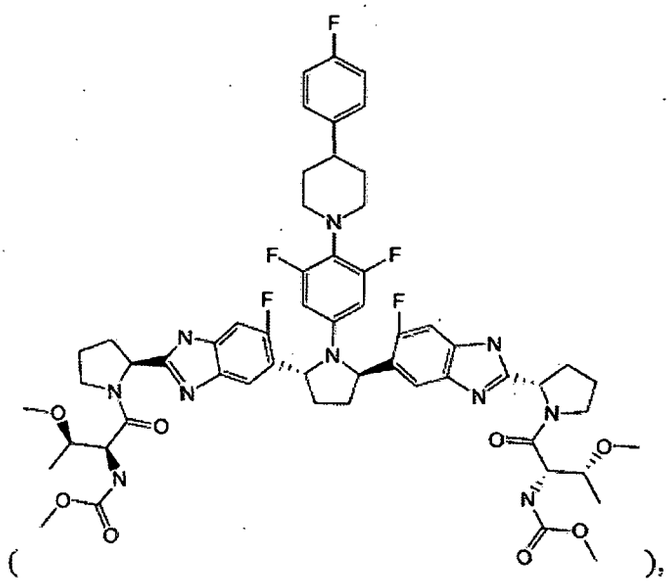
( ),

wherein the weight percentage of the one or more pharmaceutically acceptable polymers is relative to the total weight of the first composition; and

a second composition comprising:

50% to 80% by weight of one or more pharmaceutically acceptable polymers, and

40 mg Compound 2



( ),

wherein the weight percentage of the one or more pharmaceutically acceptable polymers is relative to the total weight of the second composition;

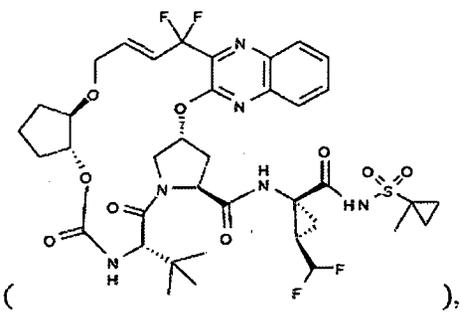
wherein the formulation is a tablet comprising a first layer and a second layer, the first layer comprising the first composition and the second layer comprising the second composition; and

wherein administration of three of the tablets to a population of healthy, fasted adult humans results in a mean AUC value between about 429 ng·h/mL and about 2431 ng/mL for Compound 1.

27. A solid oral pharmaceutical dosage formulation that is bioequivalent to a solid oral tablet pharmaceutical dosage formulation comprising

a. 500 mg of Compound 1 20% extrusion granulation, comprising:

i. 20% (100 mg) Compound 1



( ),

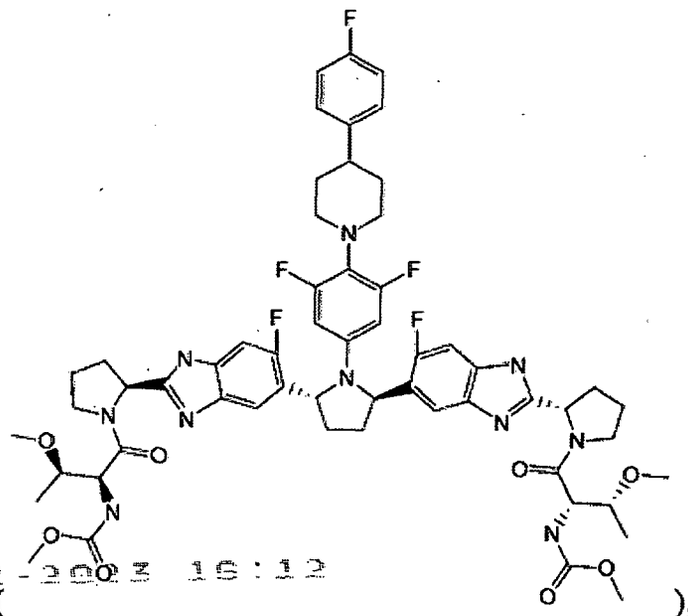
ii. 69% copovidone,

iii. 10% vitamin E TPGS, and

iv. 1% colloidal silicon dioxide;

b. 400 mg of Compound 2 10% extrusion granulation, comprising

i. 10% (40 mg) Compound 2



( ),

ii. 79% copovidone,

iii. 8% vitamin E TPGS,

iv. 2% propylene glycol monocaprylate, and

v. 1% colloidal silicone dioxide;

c. 26.3 mg croscarmellose sodium;

d. 4.7 mg colloidal silicon dioxide;

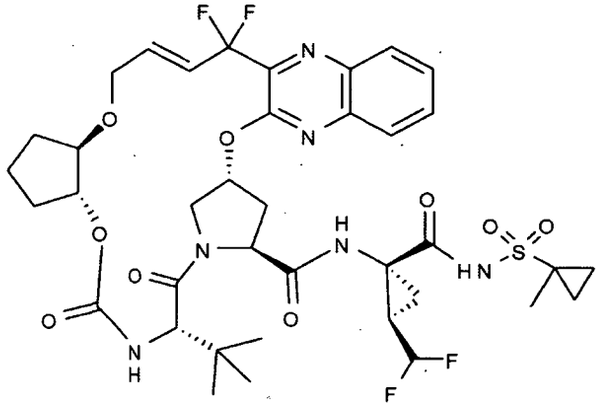
e. 4.7 mg sodium stearyl fumarate; and

f. 28.1 mg HPMC coating.

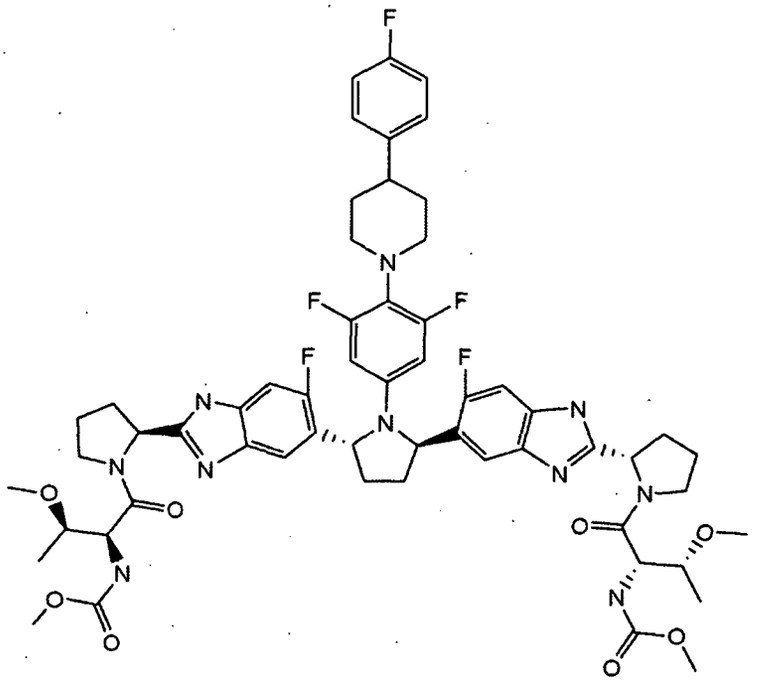
4. Impugned Patent Application: The present pre-grant opposition is against Indian Patent Application 201817002543 dated 22/01/2018 in the name of ABBVIE INC. titled "SOLID PHARMACEUTICAL COMPOSITIONS FOR TREATING HCV" and is drawn towards a solid oral pharmaceutical dosage form comprising combination of compound I (known by the INN glecaprevir) and compound II (known by the INN pibrentasvir) suitable for treatment of HCV.

5. The claimed composition for HCV treatment comprises compound I which is well known as Glecaprevir, a NS3/4A protease inhibitor as well as compound II, which is well known as Pibrentasvir, a NS5A inhibitor.

The structure of Glecaprevir is as shown below:



The structure of Pibrentasvir is as shown below:



6. Glecaprevir is also known as (3aR,7S,10S,12R,21E,24aR)-7-tert-butyl-N-{(1R,2R)-2-(difluoromethyl)-1-[(1-methylcyclopropane-1-sulfonyl)carbamoyl]cyclopropyl}-20,20-difluoro-5,8-dioxo-2,3,3a,5,6,7,8,11,12,20,23,24a-dodecahydro-1H,10H-9,12-methanocyclopenta[18,19][1,10,17,3,6]trioxadiazacyclononadecino[11,12-b]quinoxaline-10-carboxamide.

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

7. **PRIOR ARTS:** The opponent wishes to rely on the following prior arts as evidence in support of the grounds of opposition.

   i. Raymond Schinazi, Philippe Halfon, Patrick Marcellin, Tarik Asselah, "HCV direct-acting antiviral agents: the best interferon-free combinations", Liver International, 2014 Feb; 34 (Suppl 1): 69–78 (**Annexed herewith as Annexure 2**)

   ii. WO2009106960 (WO'960) published 03 September 2009 (**Annexed herewith as Annexure 3**)

   iii. WO2014152514 (WO'514) published 25 September 2014 (**Annexed herewith as Annexure 4**)

   iv. LIN C-W ET AL, "P0715 : Steady-state pharmacokinetics and safety of coadministration of pan-genotypic, direct acting protease inhibitor, ABT-493 with

pan-genotypic NS5A inhibitor, ABT-530, in healthy adult subjects", JOURNAL OF HEPATOLOGY, (201504), vol. 62, p. S592, published April 2015 (**Annexed herewith as Annexure 5**)

v. US20140080868 (US'868) published 20 March 2014 (**Annexed herewith as Annexure 6**)

vi. US8648037 (US'037) published 11 February 2014 (**Annexed herewith as Annexure 7**)

vii. US20120264780 (US'780) published 18 October 2012 (**Annexed herewith as Annexure 8**)

viii. Statement on a Non-proprietary Name Adopted by the USAN Council; Glecaprevir, published 27 May 2015 (**Annexed herewith as Annexure 9**).

ix. Statement on a Non-proprietary Name Adopted by the USAN Council; Pibrentasvir, published 27 May 2015 (**Annexed herewith as Annexure 10**).

Hepatitis C is an infectious disease caused by the hepatitis C virus (HCV). It is a type of viral hepatitis which primarily affects the liver. Chronic hepatitis C virus (HCV) infection is a leading cause of chronic liver disease. There are many active compounds which are used for treating HCV infection. These are called direct acting antiviral agents (DAAs). Mechanistically, DAAs function by inhibiting HCV non-structural proteins (NS) such as NS3/4A, NS5A, NS5B, which are vital for viral replication. Examples of DAAs are telaprevir, grazoprevir, ledipasvir, etc. Furthermore, for treatment of chronic HCV infection, a combination of two or more DAAs is administered. These are generally administered orally in the form of solid tablets, solid dispersion tablets, colloidal tablets, bi-layer tablets and so on. For multi-layered tablets, the active compounds are usually separated by an inert chemical layer to prevent any incompatible drug-drug interactions. In addition to the active compounds, the tablets also contain other non-active chemicals which are called excipients and additives. Some examples are hydrogenated vegetable oils, HPMC, sodium bicarbonate, alginic acid, copovidone, PEG, etc. HPMC in a formulation is used as a gel-forming polymer and hydrogenated vegetable oil is used as a low-density fatty excipient to contain and deliver the drug molecules. Sodium bicarbonate is used as a gas-generating agent, whereas copovidone is used as a diluent.

Schinazi et al. discloses various combinations of directly-acting antiviral agents (DAA's) being investigated for the treatment of hepatitis C infection predating the priority date of the impugned application. It is disclosed that antivirals directed at different targets including NS3/4A proteases and NS5A inhibitor are being investigated with other direct-acting antiviral agents (DAA's) for treating HCV infections. Thus, it was well-known before the priority date of the impugned application that combinations of different directly-acting antiviral agents can be envisaged for treatment of hepatitis C.

WO'960 discloses the production of bilayer tablets with a combination of antiviral agents, where three antiviral agents (Lamivudine, Efavirenz and Tenofovor disoproxil fumarate) are incorporated in bilayer tablet. The said tablet incorporates two antiviral agents in one layer and one antiviral agent in another layer to avoid potential incompatibility among the said antiviral agents. Thus, the provision of bilayer tablet to avoid potential incompatibility among active antiviral ingredients was well known before the priority date of the impugned application.

8. It is submitted that the claims of impugned patent application are liable to be refused on following grounds as below, which are without prejudice to each other:

(a) Section 25(1)(b): Lack of novelty
(b) Section 25(1)(e): Lack of inventive step
(c) Section 25(1)(f): Invention is not patentable under section 3(d), 3(e) and 3 (i)
(d) Section 25(1)(g): The complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed.
(e) Section 25(1)(h): Failure to disclose the information required by section 8 of the Patents Act.

GROUND 1: Section 25(1)(b) Lack of Novelty

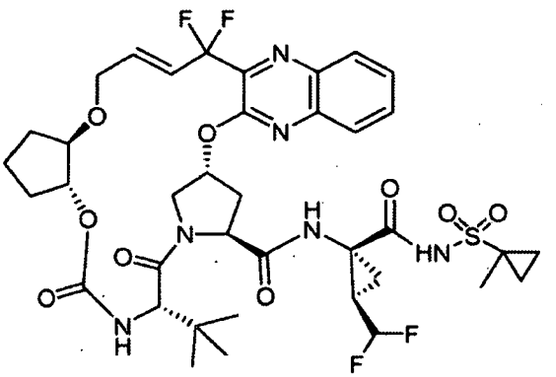
9. It is submitted that claim 1 to 27 lack novelty, and are therefore liable to be rejected under Section 25(1)(b) of the Act.

10. It is submitted that claim 1 to 27 lack novelty in view of WO'514, published on 25 September 2014.

WO2014152514 (WO'514)

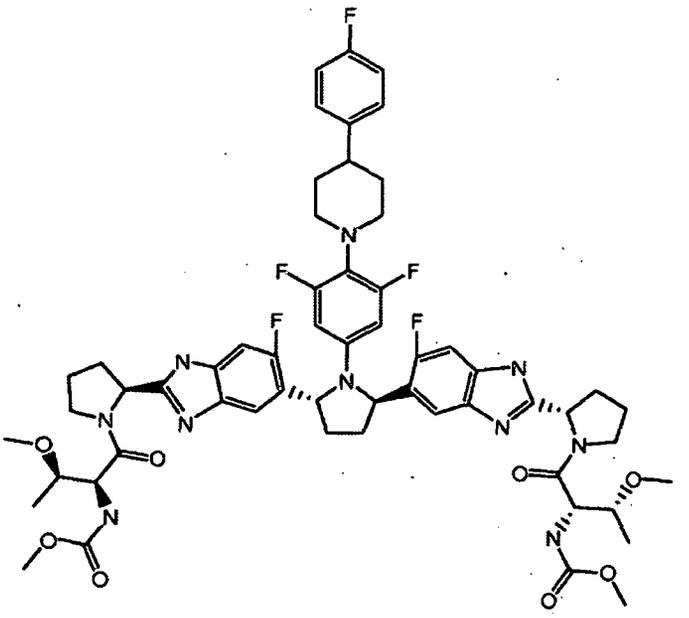
11. Opponent submits that, without prejudice, the impugned patent application lacks novelty in view of WO2014152514 (WO'514) entitled "Combination of two antivirals for treating hepatitis C", published on 25 September 2014. WO'514 discloses claimed invention in its entirety as follows:

- Administering at least two direct acting antiviral agents (DAAs) to an HCV patient. (Claim 1)
- The two DAAs comprise (a) Compound 1 or a pharmaceutically acceptable salt thereof, and (b) Compound 2 or a pharmaceutically acceptable salt thereof (Para [0007], Internal Page 2)
- Compound 1 is disclosed to have the following structure (Para [0022], Internal page 6)



This compound is Glecaprevir

- Compound 2 is disclosed to have the following structure (Para [0023], Internal page 6)



This compound is Pibrentasvir.

- It is disclosed that Compound 1 (or a pharmaceutically acceptable salt thereof) and Compound 2 (a pharmaceutically acceptable salt thereof) may be co-formulated in a single dosage form. (Para [0062], Internal page 25)
- It is disclosed that suitable dosage forms include solid dosage forms. (Para [0062], Internal page 25)
- It is disclosed that preferably Compound 1 and Compound 2 are formulated in a single solid dosage form in which at least one of the DAAs is in an amorphous form, or highly preferably molecularly dispersed, in a matrix which comprises a pharmaceutically acceptable water-soluble polymer and a pharmaceutically acceptable surfactant. The other DAAs can also be in an amorphous form or molecularly dispersed in the matrix, or formulated in different form(s) (e.g., in a crystalline form). (Para [0062], Internal page 25)
- It is further disclosed that, more preferably, each of the two DAAs is in an amorphous form, or highly preferably molecularly dispersed, in a matrix which comprises a pharmaceutically acccptable water-soluble polymer and a pharmaceutically acceptable surfactant. (Para [0062], Internal page 25)
- WO'514 also discloses the amount of compound 1 and 2 in the dosage forms which is reproduced here for ready reference-

Preferably, Compound 1 (or a pharmaceutically acceptable salt thereof) is administered from 100 mg to 600 mg once daily, and Compound 2 (or a pharmaceutically acceptable salt thereof) is administered from 50 to 500 mg once

daily. More preferably, Compound 1 (or a pharmaceutically acceptable salt thereof) is administered from 200 mg to 600 mg once daily, and Compound 2 (or a pharmaceutically acceptable salt thereof) is administered from 100 to 500 mg once daily. Highly preferably, Compound 1 (or a pharmaceutically acceptable salt thereof) is administered from 400 mg to 600 mg once daily, and Compound 2 (or a pharmaceutically acceptable salt thereof) is administered from 100 to 500 mg once daily. For instance, Compound 1 (or a pharmaceutically acceptable salt thereof) can be administered 400 mg once daily, and Compound 2 (or a pharmaceutically acceptable salt thereof) is administered 120 mg once daily. For another instance, Compound 1 (or a pharmaceutically acceptable salt thereof) can be administered 400 mg once daily, and Compound 2 (or a pharmaceutically acceptable salt thereof) can be administered 240 mg once daily."

12. Therefore, the subject matter claimed in impugned patent application is disclosed by WO' 514. Thus, claimed subject matter is anticipated and lacks novelty in view of WO' 514. Thus the impugned patent application ought to be refused on this ground alone.

GROUND 3: Section 25(1)(e) Lack of Inventive Step

13. It is submitted that the invention as claimed is obvious and does not involve any inventive step in view of the disclosures published prior to the earliest priority date of the impugned patent application i.e. prior to 26/06/2015.

14. It is submitted that claims 1-27 of the impugned application lack inventive step and are obvious in view of common general knowledge in art and combined with teachings of the following-

- WO2014152514 (WO'514)
- Lin C-W et al, "P0715 : Steady-state pharmacokinetics and safety of coadministration of pan-genotypic, direct acting protease inhibitor, ABT-493 with pan-genotypic NS5A inhibitor, ABT-530, in healthy adult subjects", JOURNAL OF HEPATOLOGY, (201504), vol. 62, p. S592, published April 2015
- US20140080868 (US'868) published 20 March 2014
- US8648037 (US'037) published 11 February 2014
- US20120264780 (US'780) published 18 October 2012

- Statement on a Non-proprietary Name Adopted by the USAN Council; Glecaprevir, published 27 May 2015
- Statement on a Non-proprietary Name Adopted by the USAN Council; Pibrentasvir, published 27 May 2015

15. It is submitted that WO'514 discloses a composition comprising the combination of two direct acting antiviral agents (DAA's) compound I and compound II, which are disclosed to be Glecaprevir i.e. compound I and Pibrentasvir i.e. compound II.

- It is further disclosed that said Compound 1 and Compound 2 may be co-formulated in a single dosage form. (Para [0062], Internal page 25) and that said suitable dosage forms include solid dosage forms. (Para [0062], Internal page 25).
- It is further disclosed that preferably Compound 1 and Compound 2 are formulated in a single solid dosage form in which at least one of the DAAs is in an amorphous form, or highly preferably molecularly dispersed, in a matrix which comprises a pharmaceutically acceptable water-soluble polymer and a pharmaceutically acceptable surfactant. Further, it is disclosed that the other DAAs can also be in an amorphous form or molecularly dispersed in the matrix, or formulated in different form(s) (e.g., in a crystalline form). (Para [0062], Internal page 25).
- It is further disclosed that, more preferably, each of the two DAAs is in an amorphous form, or highly preferably molecularly dispersed, in a matrix which comprises a pharmaceutically acceptable water-soluble polymer and a pharmaceutically acceptable surfactant (Para [0062], Internal page 25).

16. The aforesaid disclosure is to be read with Lin C-W et al. Lin C-W et al. discloses the results of a study conducted to evaluate pharmacokinetics and safety of several different dose levels of ABT-493 and ABT-530 when given in combination.

- The compounds ABT-493 and ABT-530 correspond to Glecaprevir and Pibrentasvir respectively, disclosed before the priority date of the impugned application in Annexure 9 and Annexure 10 respectively.
- Both the aforementioned compounds are disclosed to be administered in various dose combinations, one of which is combination ABT-530 at a dose of 40 mg, and ABT-493 at a dose of 100 mg.

17. Thus, WO'514 and Lin C-W et al, taken together, disclose a combination of Glecaprevir and Pibrentasvir at a dosage of 100 mg and 40 mg respectively that is co-formulated together in any suitable solid dosage form along with pharmaceutically acceptable water soluble polymer. Thus, both WO'514 *and Lin C-W et al* teach all features of independent claim 1, 24, 25, 26 and 27.

18. Moreover, a person skilled in the art would surmise that the C_{max} values claimed for compound 1 (glecaprevir) in independent claims 1 and 25 and mean AUC values for said compound claimed in claims 24 and 26 are an inherent property of the compounds once released into the gastrointestinal tract.

19. US'868 discloses method of treating HCV by administration of the compound Pibrentasvir referred to by its IUPAC name methyl {(2S,3R)-1-[(2S)-2-{5-[(2R,5R)-1-{3,5-difluoro-4-[4-(4-fluorophenyl)piperidin-1-yl]phenyl}-5-(6-fluoro-2-{(2S)-1-[N-(methoxycarbonyl)-O-methyl-L-threonyl]pyrrolidin-2-yl}-1H-benzimidazol-5-yl)pyrrolidin-2-yl]-6-fluoro-1H-benzimidazol-2-yl}pyrrolidin-1-yl]-3-methoxy-1-oxobutan-2-yl}carbamate (para [0005] and [0006], internal page 1)

- It is disclosed that said compound can be combined or co-administered with another HCV agent which includes HCV protease inhibitors (para [0008], internal page 1)
- It is further disclosed that compound I can be formulated in a solid composition in amorphous from (para [0031], internal page 4) and that such a form can be prepared through the formation of a solid dispersion with polymeric carrier (para [0032], internal page 4).
- US'868 further disclose that the compound I may be administered in a total daily dose amount of from about25 mg to about 50 mg or an amount there between. (para [0064], internal page 8).

20. US'037 discloses the compound Glecaprevir (example 6, Column 144). It is further disclosed that, in assays utilizing various HCV genotypes, compound 6 (glecaprevir) was found to be active against several HCV genotypes (para 178, lines 16-67 and para 179, lines 1-31).

- It is disclosed that compounds of the invention can be used in combination with agents that inhibit the replication of HCV by targeting proteins of the viral

genome involved in the viral replication such as HCV protease inhibitors (Column 100, lines 41-43, lines 63-67, column 101, line 7).

- It is disclosed that compounds of the invention may be administered in a dosage range of 10 to 1000mg per day in single or multiple doses (Column 115, lines 35-40)
- It is further disclosed that the compounds of invention may be administered as solid dosage forms which includes tablets (column 113, lines 22-23).

21. US'780 disclose solid compositions comprising HCV inhibitor compounds in amorphous form along with pharmaceutically acceptable hydrophilic polymer and a pharmaceutically acceptable surfactant (para [0009], internal page 2).

- It is disclosed that hydrophilic polymer utilized in the composition of invention preferably is copovidone (para [0014], internal page 3)
- It is further disclosed that the surfactant utilized in the composition of invention can be vitamin E TPGS (para [0015], internal page 3)
- US'780 further disclose that copovidone and one or more surfactants are mixed and granulated, followed by the addition of aerosil and compound of the invention. (para [0064], internal page 9). It is submitted that aerosil is a trade name for colloidal silicon dioxide and has been well known much before the priority date of the impugned application.
- It is disclosed that propylene glycol monocaprylate may be utilized in solid compositions of the invention (para [0047], internal page 7).
- It is further disclosed that sodium croscarmellose may be utilized in the formulation as well as sodium stearyl fumarate (para [0071], internal page 10).
- It is further disclosed that tablet formulation may be coated utilizing a polymeric film-forming material such as hydroxypropyl methylcellulose which is also known as HPMC (para [0075], internal page 10).
- It is disclosed that the compounds of the invention may be formulated as extrudates by the process of granulating (polymer, surfactant and aerosil plus compound) followed by extrusion of mixture (para [0064], internal page 9).

22. Thus, US'780 discloses and teaches all features of a solid oral pharmaceutical dosage form claimed in claim in the impugned application.

23. In light of the common general knowledge, a person skilled in the art knows that combining two active ingredients may cause incompatibility. The best way to avoid any chances of incompatibility is to create a layer between them so that they cannot react to each other. Therefore, a person skilled in the art without taking any risk of incompatibility he/she would select a bi-layer concept like bi-layer solid dosage form or bi-layer tablet.

24. In the impugned patent application, both the active compounds were already known in the public domain. It is also known that active compounds can be given orally, such as solid tablets or solid dispersion tablets. Furthermore, it is common practice that, when two or more active compounds are administered together, they need to be separated in order to reduce chances of incompatibility, which is usually done by having a bilayer tablet with an inert layer of silicon dioxide in between the layers. Thus, from prior arts review, an ordinary person skilled in the art, would be able to arrive at the known active molecules given in the impugned patent application. Furthermore, the person would also know that a combination of the compounds can be used, which could be administered orally. Moreover, as discussed in the previous paragraph, the person would know that the two active compounds have to be separated using an inert layer. In addition, the person would know to use additives in the tablet in case of oral administration for use as a diluent for better uptake and bioavailability. Thus, the subject matter claimed in impugned patent application is obvious and lacks inventive step. In view of the above submissions, impugned application lacks inventive step and therefore, should be rejected on this ground alone.

GROUND 3: Claims not patentable under Section 25(1)(f)

The claimed subject matter in not patentable under Section 3(d) of the Act

25. It is submitted that the impugned patent application falls within the purview of section 3(d) of the Patents Act, 1970 which states that *"the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant.*

Explanation -For the purposes of this clause, salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes,

combinations and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy."

26. It is humbly submitted that the claims of the impugned patent application are directed to a solid oral dosage formulation of two known drugs Glecaprevir and Pibrentasvir. The said combination with specific doses was already disclosed by Lin C-W et al. The Applicant fails to provide any enhanced therapeutic efficacy data in relation to known efficacy. Therefore, in light of this the patent application should be rejecting.

27. The complete specification discloses that the two drugs are formulated such that they exist in separate layers and physically do not interact with each other in the formulations described in the specification. Therefore, the formulations claimed are simply a new form of known substances and fall within the purview of section 3(d) of the Patents Act.

28. It is further submitted that the Applicant has contended in their reply to the FER that *"an incomplete in vitro release of compound 2 has been observed from a tablet in which compound 1 and compound 2 are co-blended, suggesting a physical drug-drug interaction between compounds 1 and 2. In contrast, however, substantially complete in vitro release of compound 2 can be achieved using a bilayer tablet in which compound 1and compound 2 are present in separate amorphous solid dispersions in two layers.*

Thus, a solid dosage form according to the present claim 1 can perform better than a comparable dosage form in which the compounds are formulated in the same solid dispersion. This is not taught or suggested in the cited documents.

29. At the outset, it is humbly submitted that an vitro dissolution profile demonstrating a better dissolution performance as stated by the Applicant in the above statement does not constitute a demonstration of enhanced therapeutic efficacy as per section 3(d) of the Patents Act.

30. Secondly, it is submitted that, as elaborated above, Applicant has contended that the two drugs glecaprevir and pibrentasvir, formulated separately in bilayer tablets have better in release as compared to a dosage form in which both drugs are formulated together due to drug-drug interaction. However, no data has been presented in the

complete specification comparing drug release from both drugs co-formulated together in same dosage form with the same drugs formulated separately in same dosage form. The comparative data actually presented in the specification on drug release (Example 3, para [00100]- para [0103], internal page 22-25) shows that the study has been conducted comparing drug release from bilayer tablet (Regimen A, B and C) with drug release from separately administered tablets (Regimen D).

The said regimen is shown below:

Regimen A	Single dose of Compound 1/Compound 2 film-coated bilayer tablets 300 mg/120 mg (3 × 100 mg/40 mg) given under fasting conditions
Regimen B	Single dose of Compound 1/Compound 2 film-coated bilayer tablets 300 mg/120 mg (3 × 100 mg/40 mg) given with a moderate fat breakfast
Regimen C	Single dose of Compound 1/Compound 2 film-coated bilayer tablets 300 mg/120 mg (3 × 100 mg/40 mg) given with a high fat breakfast
Regimen D	Single dose of Compound 1 tablets (300 mg, 3 × 100 mg tablets) and Compound 2 tablets (120 mg, 3 × 40 mg tablets) given under fasting conditions

The pharmacokinetic parameters (geometric mean) of compound 1 obtained after following the above regimen is shown below:

Pharmacokinetic Parameters	Units	Regimen A (N=23)	Regimen B (N=23)	Regimen C (N=23)	Regimen D (N=23)
C_{max}	ng/mL	294 (384, 78)	937 (1193, 84)	633 (723, 54)	803 (973, 72)
T_{max} [a]	h	3.0 (1.5 to 5.0)	4.0 (3.0 to 5.0)	5.0 (4.0 to 6.0)	2.0 (1.0 to 3.0)
$t_{1/2}$ [b]	h	6.0 (24)	6.0 (16)	6.3 (18)	5.7 (16)
AUC_t	ng·h/mL	1150 (1430, 70)	3040 (3460, 60)	2110 (2390, 54)	2620 (2970, 53)
AUC_{inf}	ng·h/mL	1150 (1440, 69)	3040 (3470, 60)	2120 (2390, 54)	2620 (2980, 53)

From the above it is apparent that the C_{max} and AUC of regimen D (corresponding to separate administration of glecaprevir and pibrentasvir tablets) is actually higher than the C_{max} and AUC of regimen A and regimen C (which corresponds to fixed dose film-coated bilayer tablets of glecaprevir and pibrentasvir). Therefore, even considering the parameter of enhanced C_{max} and AUC, the performance of separately administered tablets outstrips that of bilayer tablet comprising both drugs.

Thus, an enhanced drug release profile has not been demonstrated in impugned application.

31. Thus, no in vivo data has been presented in the complete specification for demonstrating any kind of enhanced therapeutic efficacy of the claimed composition over the drugs administered either separately or in same dosage form.

32. Thus, it is humbly submitted that the Impugned application falls squarely within the purview of section 3(d) of the Patents Act 1970 and ought to be rejected.

The claimed subject matter in not patentable under Section 3(e) of the Act

33. It is submitted that the impugned patent application falls within the purview of section 3(e) of the Patents Act, 1970 which states that "*a substance obtained by a mere admixture resulting only in the aggregation of the properties of the components thereof or a process for producing such substance*".

34. It is humbly submitted that, as elaborated in preceding paragraph, the claims of the impugned patent application are directed to a solid oral dosage formulation of two known drugs Glecaprevir and Pibrentasvir. The complete specification discloses that the two drugs are formulated such that they exist in separate layers and physically do not interact with each other in the formulations described in the specification. Therefore, the formulations claimed are simply an admixture of known substances and fall within the purview of section 3(e) of the Patents Act. No synergistic effect of the combined administration of glecaprevir and pibrentasvir from film-coated bilayer tablets has been demonstrated.

35. Thus, it is submitted that the impugned application falls within the purview of section 3(e) of the Patents Act, 1970 and should be refused on the said ground.

The claimed subject matter in not patentable under Section 3(i) of the Act

36. It is submitted that the impugned patent application falls within the purview of section 3(i) of the Patents Act, 1970 which states that "*any process for the medicinal, surgical, curative, prophylactic [diagnostic, therapeutic] or other treatment of human*

beings or any process for a similar treatment of animals to render them free of disease or to increase their economic value or that of their products."

37. It is submitted that the independent claims 1, 24, 25 and 26 claim a solid oral pharmaceutical dosage form, with the limitation that the administration of tablets of drug combination claimed in impugned application to a certain population results in certain C_{max} values (see claims 1 and 25) or results in certain AUC values (see claims 24 and 26) by the administration of three tablets to a population of healthy, non-fasted adult humans (claim 1 and 24), or by administration of three tablets to a population of healthy, fasted adult humans (claim 25 and 26).

38. It is submitted that the above limitation of achieving a certain C_{max} value or AUC value by administration of a certain number of tablets is just a process for the medicinal treatment of human beings.

39. Thus, it is humbly submitted that the impugned application falls within the purview of section 3(i) of the Patents Act, 1970 and should be refused on the said ground.

GROUND 4: INSUFFICIENCY OF DISCLOSURE

40. It is submitted that complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed.

41. It is submitted that it is a well settled law that the specification should clearly and fairly describe the invention and disclose the best mode of working the invention so that the person skilled in the art could perform the invention without any undue efforts. Further, it is submitted that claims of impugned application are not fairly based on the specification and the complete specification does not fairly describe the invention and the method by which it is to be performed.

42. It is submitted that claim 1 and claim 25 discloses mean Cmax values wherein claim 1 directs "mean Cmax value between about 333 ng/ml and about 1113 ng/mL for compound 1" and "mean Cmax value between about 85 ng/ml and about 684 ng/mL for compound 1" in claim 25. Opponent submits that the said claims are not supported by impugned application. Because table 5a discloses pharmacokinetic parameters for compound 1 wherein Cmax values lies between 294 to 937.

Therefore, the higher limit of Cmax which is 1113 is outside the range and similarly the lower limit of Cmax which is 85 for claim 25 also falls outside the range.

43. On similar lines claim 24 and claim 26 discloses mean AUC values wherein claim 1 directs "AUC value between about 1099 ng.h/mL and about 3680 ng/mL for compound 1" and "AUC value between about 429 ng.h/mL and about 2431 ng/mL for compound 1" in claim 24. Opponent submits that the said claims are not supported by impugned application. Because table 5a discloses pharmacokinetic parameters for compound 1 wherein AUC value lies between 1150 to 3040. Therefore, the higher limit of AUC which is 3680 is outside the range and similarly the lower limit of AUC which is 429 for claim 26 also falls outside the range.

44. It is submitted that the complete specification discloses clinical trials to determine bioavailability and food effect of compound 1/compound 2 film-coated bilayer tablets. (Example 3, para [00100], internal page 22). The result of this study is disclosed as showing that "*administration with food significantly improved the bioavailability of both Compound 1 and Compound 2, and the improvement was achieved with regard to the fat content in the food.*" (para [0103], internal page 24).

45. However, if the trial shows that the very important parameter of bioavailability depends on effect of food and the fat content of food, it introduces a large amount of variability with respect to bioavailability as the food intake and food content of different patients taking the drug combination is sure to vary as people do not all have the same type of food and same content of food. Such an effect has not been quantified nor has the formulation standardised to deal with such food effect in the complete specification.

46. The complete specification contains a mere statement that administration with food significantly improved the bioavailability of both Compound 1 and Compound 2, and the improvement was achieved with regard to the fat content in the food (para [0103], internal page 24), However, since the significant improvement with respect to food referred to above has not been quantified, i.e. person of ordinary skill in the art would have to rely on undue experimentation to determine the type and content of food to achieve significant bioavailability. Indeed, given the uncertain nature of food intake in different individuals, the bioavailability might even reduce due to

different type of foods in different populations. Such an effect has not been accounted for in the specification.

47. It is submitted that claim 1 (amended claim currently on record) includes a second composition comprising compound 2 and 50% to 80% by weight of one or more pharmaceutically acceptable polymers.

In the PCT publication through which the current application entered the national phase in India, in claim 1, claimed compound 2 'formulated in amorphous solid dispersion which further comprises from 50% to 80% by weight of a second pharmaceutically acceptable polymer'. Therefore, the amended claim is broader than the claim 1 with which the impugned application was entered in the national phase.

However, the complete specification only describes the preparation of formulations in the form of solid dispersions and fails to support the broader limitation directed to composition with compound 2 and 50% to 80% by weight of one or more pharmaceutically acceptable polymers.

48. The specification discloses that the administration of the claimed bilayer tablets comprising compound 1 and compound 2 shows improved bioavailability with food. However, the data disclosed shows that the AUC of individual tablets administered in the fasted condition (regimen D - Table 5b) is higher than with food (regimen B and C) depicted below:

Pharmacokinetic Parameters	Units	Regimen A (N=23)	Regimen B (N=23)	Regimen C (N=23)	Regimen D (N=23)
C_{max}	ng/mL	116 (140, 60)	221 (239, 44)	237 (262, 45)	175 (192, 38)
T_{max} [a]	h	4.0 (2.0 to 5.0)	5.0 (3.0 to 5.0)	5.0 (4.0 to 6.0)	4.0 (2.0 to 5.0)
$t_{1/2}$ [b]	h	13.3 (9)	13.0 (10)	13.5 (9)	12.5 (8)
AUC_t	ng·h/mL	910 (1100, 64)	1280 (1400, 49)	1390 (1560, 49)	1420 (1570, 40)
AUC_{inf}	ng·h/mL	960 (1160, 64)	1350 (1480, 49)	1460 (1650, 50)	1490 (1650, 40)

It is submitted that this is in direct contradiction to the contention in the specification with respect to the effect of food on improved bioavailability of compound 1 and compound 2.

GROUND 5: INFORMATION RELATING TO CORRESPONDING APPLICATIONS UNDER SECTION 8 [SECTION 25(1)(H)]

49. The Applicant has failed to disclose to the Patent Office the information required under Section 8.The Applicant is required to provide all the information regarding the prosecution of the equivalent applications till the grant of the Indian application to the Patent Office in writing from time to time and also within the prescribed time.

50. It is observed that Applicant has not provided information about updated the status of corresponding application in the Form-3 which information has not been provided to the learned Controller.

51. Therefore, the applicant has failed to comply with the requirements of the section 8 of the act and the opponent demands rejection on this ground also.

52. It is submitted that the Applicant has failed to disclose the details of corresponding foreign applications and impugned patent application to be refused.

53. The opponents crave leave to file further submissions and evidence with respect to this ground.

CONCLUSION

54. In view of the above, the claims are not novel, inventive and not patentable and insufficient. The pre-grant opposition as filed may be allowed and the subject patent application may be refused.

HEARING REQUESTED

55. The Opponent hereby requests a hearing under section 25(1) of the Patents Act, 1970 (hereinafter referred to as "the Patents Act") and Rule 55 of the Patents Rules (hereinafter referred to as "the Rules").

PRAYER

In the fact and circumstances of the case, the Opponent prays as follows:

i. that the Controller take the present Opposition on record; that the Indian application 201817002543, be rejected under Section 25(1) of the Patents (Amendment) Act, 2005;

ii. that the Opponent may be allowed to file further documents and evidence if necessary to support their averments;

iii. that the Opponent may be allowed to file rejoinder and affidavit if necessary to support their averments;

iv. that the Opponent may be granted an opportunity of being heard in the matter before any final orders are passed;

v. that the Opponent may be allowed to make further submissions in case the Applicant makes any amendments in the claims;

vi. any other reliefs considering the facts and circumstances may be granted in favour of the Opponent in the interest of justice.

Dated this 28th day of December, 2022

RAJESHWARI H. IN/PA - 0358
OF RAJESHWARI AND ASSOCIATES
AGENT FOR THE OPPONENT

TO
THE CONTROLLER OF PATENTS
THE PATENT OFFICE, NEW DELHI