

**BEFORE THE CONTROLLER OF PATENTS, THE PATENT OFFICE, DELHI
THE PATENTS ACT, 1970 AND THE PATENTS RULES, 2003**

IN THE MATTER OF A PRE- GRANT OPPOSITION UNDER SECTION 25 (1)
AND RULE 55 OF THE PATENTS ACT, 1970

And

IN THE MATTER OF PATENT APPLICATION NO. 806/DELNP/2010 DATED
FEBRUARY 02, 2010 IN THE NAME OF BRISTOL-MYERS SQUIBB HOLDINGS
IRELAND OF HINTERBERGSTRASSE 16, 6312, STEINHAUSEN, SWITZERLAND.

....APPLICANT/RESPONDENT

And

IN THE MATTER OF REPRESENTATION BY WAY OF NOTICE OF OPPOSITION
FILED BY THE DELHI NETWORK OF POSITIVE PEOPLE (DNP+) AND THE
INITIATIVE FOR MEDICINES, ACCESS & KNOWLEDGE, INC (I-MAK)

.....OPPONENTS/PETITIONERS

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STATEMENT OF CASE OF THE OPPONENTS

1. The Opponents are the Delhi Network of Positive People (DNP+), a community based non-profit organisation representing the needs of people living with HIV/AIDS (“PLHAs”) and Hepatitis C (HCV), registered as a Trust under Registration No. 8525, Additional Book No. 1423/1-23 IV Sub Registrar, New Delhi, with its registered address at Flat no. A1-5, Property 141 Gali No. 3, Harijan Colony, Neb Sarai, New Delhi, 110068 and the Initiative for Medicines, Access & Knowledge (I-MAK), Inc, a not-for-profit public service organisation comprising lawyers and scientists working to protect the public domain against undeserved patents to ensure they do not act as a barrier to research and restrict public access to affordable medicines, having its registered address at 16192 Coastal Highway, Lewes, Delaware, 19958-9776, U.S.A. The Opponents make the following representation under Section 25(1) of the Act in opposing the grant of a patent for the application indicated in the cause title.

2. ANALYSIS OF THE APPLICANT'S SPECIFICATION

2.1 The Patent Application No. 806/DELNP/2010 ('806) titled "Crystalline form of methyl ((1s)-1-(((2s)-2-(5-(4'-(2-((2s)-1-((2s)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1h-imidazol-5-yl)-4-biphenyl)-1h-imidazol-2-yl)-1-pyrrolidinyl) carbonyl)-2-methylpropyl) carbamate dihydrochloride salt". '806 was filed in India on February 05, 2010. '806 is a national phase application stemming from PCT Application No. PCT/US2008/071734 (published as WO2009/020828), filed on July 31, 2008 and published on February 12, 2009. PCT Application No. PCT/US2008/071734 claims priority from United States patent application US 60/954,592 filed on August 08, 2007. '806 was published in the Official Journal of the Patent Office, Journal No. 31/2010, page 22262 on July 30, 2010 in accordance with Section 11A of the Patents Act. A copy of the Journal publication is attached as **Exhibit 1**. The request for examination of '806 was filed on January 11, 2011 under Section 11B of the Act & Rule 24B (1) (i) of the Rules.

2.2 Based on the information provided by the Indian Patent Office database, inPASS, '806 is currently under examination. Accordingly, as provided under Section 25(1) of the Act read with Rule 55(1), any person may file a representation by way of opposition at the appropriate office (Delhi) before the grant of a patent. The Opponents submit their opposition and supporting evidence to '806 based on the grounds set out below. Under the above provisions, the Opponents also request a hearing before this matter is finally decided.

3. BACKGROUND TO '806

3.1 The Hepatitis C virus (HCV) presents a serious global health problem. The virus is transmitted through direct contact with an infected person's blood. Persons with needle-stick injury, health care workers with exposure to blood/blood products, transfusion/blood product recipients, organ transplant recipients and intravenous drug users are some of the populations at risk from HCV. According to the World Health Organization, over 80 million people have chronic HCV infection and are likely to develop liver cancer and/or cirrhosis. The best estimates available show India alone has an estimated 6 million people who are chronically infected with HCV, with 96,000 deaths

annually due to the infection. India is also home to 2.1 million people living with HIV (PLHIV) and applying the global co-infection rate of 2.4% implies that approximately 50,400 people in this community may be co-infected with HCV.

3.2 Given the public health crisis around HCV, it is imperative that people living with HCV are able to access the latest and most effective treatments without unmerited patents standing in the way. Undeserved patents of the nature applied for in '806 affords a company, such as the Applicant, artificial exclusive rights, which then allows it to price a medicine beyond the reach of not only Indian patients, but also many in need in other developing and even developed countries. The Applicant also strategically uses such unmerited patents in its licensing programme in India in order to manage the generic competition and further delay legitimate open competition. By managing the competition, the Applicant is able to control the market in India but also in other countries where competitors may otherwise have been able to sell the medicine at more affordable prices.

3.3 The invention claimed in '806 covers a crystalline form of methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl) carbonyl)-2-methylpropyl) carbamate dihydrochloride salt, pharmaceutical compositions comprising the crystalline form, methods of using the crystalline form in the treatment of HCV and methods for obtaining the crystalline form.

3.4 The problem which '806 seeks to resolve is that the compound "methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl) carbonyl)-2-methylpropyl) carbamate cannot be easily crystallized and, therefore, a product with high purity cannot be obtained. The alleged solution claimed in '806 is obtaining a dihydrochloride salt of Compound (I), specifically as a polymorphic form referred as "Form N-2", and which offers high aqueous solubility and purity.

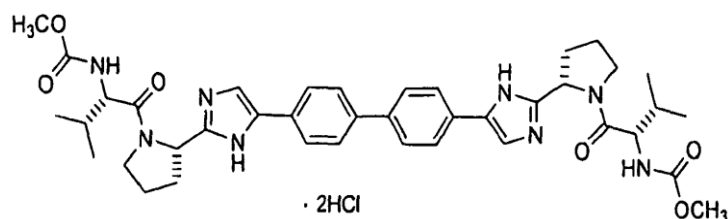
3.5 According to documents made available on the Patent Office website, the initial filing of '806 on February 5, 2010 comprised 20 claims relating to a crystalline form of methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-

pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate dihydrochloride salt, pharmaceutical compositions comprising the crystalline form, methods of using the crystalline form in the treatment of HCV and methods for obtaining the crystalline form.

3.6 On the same day of filing the application, the Applicant submitted a more specific set of Claims, attached as **Exhibit 2**. '806 now comprises 12 Claims. Claim 1 is the independent claim, and the remainder of the Claims 2 to 12 are dependent claims. The Opponents believe that the Claims as set out in Exhibit 2 are the ones that the Applicant wishes to be examined. Accordingly, the Opponents set out their grounds of opposition against the same. However, should the Applicant amend any of its Claims during examination, the Opponents reserve their right to modify the present opposition at that stage and/or file a supplementary opposition.

3.7 The current set of Claims for '806 as set out in **Exhibit 2** may be summarised as follows:

1. Claim 1 covers Form N-2 of



characterized by one or more of the following:

a) a unit cell with parameters substantially equal to the following:

Cell dimensions: $a = 7.5680 \text{ \AA}$

$b = 9.5848 \text{ \AA}$

$c = 16.2864 \text{ \AA}$

$\alpha = 74.132 \text{ degrees}$

$\beta = 84.132 \text{ degrees}$

$\gamma = 70.646 \text{ degrees}$

Space group P1

Molecules/unit cell 1

wherein measurement of said crystalline form is at a temperature between about 20°C to about 25 °C; b) characteristic peaks in the powder X-Ray diffraction pattern at values of two theta of 10.3 ± 0.1 , 12.4 ± 0.1 , 12.8 ± 0.1 , 13.3 ± 0.1 , 13.6 ± 0.1 , 15.5 ± 0.1 , $20.3 \pm$

0.1, 21.2 ± 0.1 , 22.4 ± 0.1 , 22.7 ± 0.1 , and 23.7 ± 0.1 at a temperature between about 20°C and about 25 °C; and/or

c) a melt with decomposition endotherm with onset typically in the range of 225-245 °C.

2. Claim 2 is dependent on Claim 1 and covers the form of Claim 1 having a purity of at least 90 weight percent.

3. Claim 3 is dependent on Claim 2 and covers the form of Claim 2 having a purity of at least 95 weight percent.

4. Claim 4 is dependent on Claim 2 and covers the form of Claim 2 having a purity of at least 99 weight percent.

5. Claim 5 covers a pharmaceutical composition comprising Form N-2 according to any one of Claims 1 to 4 and a pharmaceutically acceptable carrier or diluent, optionally in combination with one or two additional compounds having anti-HCV activity.

6. Claim 6 is dependent on Claim 5 and covers the pharmaceutical composition of Claim 5 wherein said Form N-2, if combined with one or two additional compounds having anti-HCV activity, has a purity of at least 90 weight percent.

7. Claim 7 is dependent on Claim 6 and covers the pharmaceutical composition of Claim 6 wherein said Form N-2, if combined with one or two additional compounds having anti-HCV activity, has a purity at least 95 weight percent.

8. Claim 8 is dependent on Claim 6 and covers the pharmaceutical composition of Claim 6 wherein said Form N-2, if combined with one or two additional compounds having anti-HCV activity, has a purity at least 99 weight percent.

9. Claim 9 covers the composition of any one of Claims 5 to 8 wherein at least one of the additional compounds having anti-HCV activity is an interferon or ribavirin.

10. Claim 10 is dependent on Claim 9 and covers the composition of Claim 9 wherein the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastoid interferon tau.

11. Claim 11 is dependent on Claim 5 and covers the composition of Claim 5 wherein at least one of the additional compounds is selected from interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA, Imiquimod, ribavirin, an inosine 5'-monophosphate dehydrogenase inhibitor, amantadine, and rimantadine.

12. Claim 12 covers a compound of any one of Claims 1 to 4 for use in a method of treating HCV infection.

4.GROUNDS OF OPPOSITION

4.1 Based on the claims set out above, the Opponents submit that Claims 1 to 12 are not patentable under the following grounds of Section 25(1) of the Act:

a. SECTION 25 (1) (c): ANTICIPATION BY PRIOR CLAIMING

That the invention so far as claimed in any claim of the complete specification published on or after priority date of the Applicant's claim and filed in pursuance of an application for a patent in India, being a claim of which the priority date is earlier than that for the applicant's claim.

b. SECTION 25(1)(e): OBVIOUSNESS/LACK OF INVENTIVE STEP

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.

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

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, in particular under Section 3(d).

d. SECTION 25 (1) (g): INSUFFICIENT DESCRIPTION

That the complete specification does not sufficiently and clearly describe the invention or the method by which it is performed.

e. **SECTION 25 (1) (h): NOT COMPLIED WITH THE REQUIREMENTS OF SECTION 8**

That the Applicant has failed to disclose to the Controller the information required by Section 8 or has furnished the information that in any material particular was false to his knowledge.

f. **SECTION 25 (1) (i): NOT FILED WITHIN 12 MONTHS AS REQUIRED IN CONVENTION APPLICATION.**

That the convention application was not filed in India within twelve months from the date of the basic application in the convention country from which priority is claimed.

4.2 PRIOR ART REFERENCES

The Opponents rely on the following prior art references for the purpose of this opposition:

- a. 853/DELNP/2009 ('853) titled "Hepatitis C virus inhibitors", Bristol-Myers Squibb company, Priority date August 11, 2006, published June 12, 2009 marked as **D1**.
- b. WO2006/133326A1 (WO '326) titled "Inhibitors of HCV replication", Bristol-Myers Squibb company, published December 14, 2006, marked as **D2**.
- c. WO2007/031791A1 (WO '791) titled "Biphenyl derivatives and their use in treatment of hepatitis", Arrow Therapeutics Limited, published March 22, 2007 marked as **D3**.
- d. Hermann. S *et al.*, "Synthesis of aromatic-linked 4(5), 4' (5')-diimidazoles, *Journal of Practical Chemistry*, 4 series, Volume 22, published 1963, marked as **D4**.
- e. WO2003/062265 (WO '265) titled as "Novel peptides as NS3 serine protease inhibitors of hepatitis C virus", Schering corporation, published July 31, 2003), marked as **D5**

- f. Chao Lin, HCV NS3-4A Serine Protease, Hepatitis C Viruses Genomes and Molecular Biology, *Horizon Bioscience*, Seng-Lai Tan ed, published 2006, marked as **D6**.
- g. US2005/0020590 (US '590) titled "P38 Kinase inhibitors", published January 27, 2005, marked as **D7**.
- h. Gould, P.L., "Salt selection for basic drugs", *International Journal of Pharmaceutics*, vol. 33, pp 207-217, published 1986, marked as **D8**.
- i. Bighley. L *et al.*, "Encyclopaedia of Pharmaceutical Technology", vol. 13, pages: 453 – 499, published 1995, marked as **D9**.
- j. Guillory, J. K., "Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids," Chapter 5 in Polymorphism in Pharmaceutical Solids, Brittain, H. G., Ed., vol. 95 of Drugs and the Pharmaceutical Sciences, Marcel Dekker, Inc., New York, NY, 1999, pp. 183-226, published 1999 marked as **D10**.
- k. International Conference on Harmonisation: Guidance on Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances, Federal Register, Vol 65, No. 251, published December 29, 2000, marked as **D11**.
- l. Byrn, S., et al., "Pharmaceutical Solids: A Strategic Approach to Regulatory Considerations", *Pharmaceutical Research*, col. 12, no. 7, pp. 945-954, published 1995, marked as **D12**.

5.DETAILED GROUNDS

5.1 GROUND I

Claims 1 to 12 of '806 are not new, lack novelty, are anticipated by prior publication and, therefore, should be rejected under Section 25(1) (c) and 2(1)(l) of the Patents Act.

5.1.1. Section 25(1) (c) provides that a patent can be opposed on the ground that the invention so far as claimed in any claim of the complete specification is claimed in a claim of a complete specification **published on or after the priority date of the Applicant's claim** and filed in pursuance of an application for a patent in India, being a

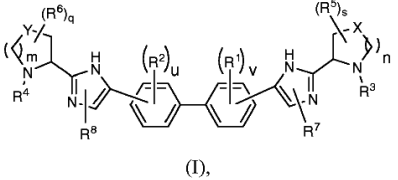
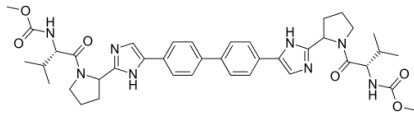
claim of which the **priority date is earlier than that of the Applicant's claim**. It is submitted that all the claims of '806 should be rejected on the ground of anticipation by prior claiming. The Opponents state that Claims 1 to 12 of '806 already form part of the subject matter of an earlier application '853 (D1) filed by the same Applicant.

5.1.2 853/DELNP/2009 ('853) titled "Hepatitis C virus inhibitors", Bristol-Myers Squibb company, Priority date August 11, 2006, published June 12, 2009 marked as D1.

(a) '853 (D1) titled "Hepatitis C Virus inhibitors" was filed in India on February 05, 2009. '853 is the national phase entry of WO2008021927A2 ('927) (attached as **Exhibit 3**) and was published under Section 11A in the Official Journal No. 24/2009 of the Indian Patent Office on June 12, 2009. '853 claims priority from two US provisional applications: US 60/836, 999 filed on August 11, 2006 and US 11/835,462 filed on August 8, 2007. Therefore, for the purpose of Section 25(1)(c), the earliest priority date of '853 is August 11, 2006 pre-dates the priority date of August 08, 2007 as claimed in '806.

(b) The Opponents submit that the alleged invention claimed in '806 forms the subject matter of the earlier patent application '853. It is submitted that all the Claims of '806 are encompassed or even directly claimed in the Claims of '853. The comparison of the Claims of '806 with the Claims of '853 is provided in Table 1 below for the sake of clarity and convenience.

Table 1: Comparison of the Claims of patent application '806 vis-à-vis Claims of '853 patent application.

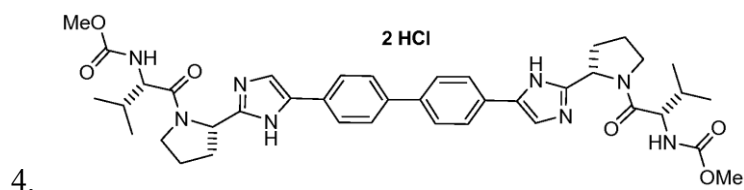
853/DELNP/2009 ('853)	806/DELNP/2010('806)
<p>Claim 1 of '853 covers the compound of daclatasvir <u>or a pharmaceutically acceptable salt thereof</u>:</p> <p>A compound of formula (I)</p>  <p>(I),</p> <p>When X and Y =CH₂ R⁷= H; R³ and R⁴ =R⁹-C(O)- where R⁹ = (NR^cR^d)alkyl</p>	<p>Form N-2 of</p>  <p>Claim 1 of '806 only includes the additional feature of powder X-ray diffraction peaks.</p>
<p>Claim 23 of '853 expressly claims the compound of daclatasvir <u>or a pharmaceutically acceptable salt thereof</u>:</p> <p><i>A compound which is methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1 H-imidazol-2-yl)- 1 - pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate; or a pharmaceutically acceptable salt thereof.</i></p>	<p>2.Claims 5-8 cover a pharmaceutical composition of Form N-2 of daclatasvir.</p>
<p>3.Claim 35 of '853 read with claim 1 covers a pharmaceutical composition comprising <i>methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1 H-imidazol-2-yl)- 1 -</i></p>	<p>Claims 1 to12</p>

<p><i>pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate or a pharmaceutically acceptable salt, and a pharmaceutically acceptable carrier</i></p>	
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A review of the comparative data provided in Table 1 above reveals that the subject matter as claimed in Claims 1 to 12 of '806 is expressly encompassed within the Claims of '853.

(c) The Opponents submit that on pages 157-159, Example 24-23 of '853, '853 specifically discloses the preparation of **daclatasvir dihydrochloride** and its **recrystallization**. The relevant portion is reproduced below:

“Example 24-23



methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl) -1 - pyrrolidinyl) carbonyl) -2-methylpropyl) carbamate

A 50 mL flask equipped with a stir bar was sequentially charged with 2.5 mL acetonitrile, 0.344 g (2.25 mmol, 2.5 equiv) hydroxy benzotriazole hydrate, 0.374 g (2.13 mmol, 2.4 equiv) N-(methoxycarbonyl)-L-valine, 0.400 g (2.09 mmol, 2.4 equiv) 1 -(3 - dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and an additional 2.5 mL acetonitrile. The resulting solution was agitated at 20 °C for 1 hour and charged with 0.501 g (0.88 mmol, 1 equiv) Example A-le-4. The slurry was cooled to about 0 °C and 0.45 g (3.48 mmol, 4 equiv) diisopropylethylamine was added over 30 minutes while maintaining a temperature below 10 °C. The solution was slowly heated to 15 °C over 3 hours and held at 15 °C for 16 hours. The temperature was increased to 20 °C and stirred for 3.25 hours. The resulting solution was charged with 3.3 g of 13 wt% aqueous NaCl and heated to 50 °C for 1 hour.

After cooling to 20 °C, 2.5 mL of isopropyl acetate was added. The rich organic phase was washed with 2 x 6.9 g of a 0.5 N NaOH solution containing 13 wt% NaCl followed by 3.3 g of 13 wt% aqueous NaCl. The mixture was then solvent exchanged into isopropyl acetate by vacuum distillation to a target volume of 10 mL. The resulting hazy solution was cooled to 20 °C and filtered through a 0.45 µm filter. The clear solution was then solvent exchanged into ethanol by vacuum distillation with a target volume of 3 mL. 1.67 mL (2.02 mmol, 2.3 equiv) of 1.21 M HCl in ethanol was added. The mixture was then stirred at 25 °C for 15 hours. The resulting slurry was filtered and the wet cake was washed with 2.5 mL of 2: 1 acetone:ethanol. The solids were dried in a vacuum oven at 50 °C to give 0.550 g (0.68 mmol, 77 %) of the desired product.

Recrystallization of Example 24-23

A solution of Example 24-23 prepared above was prepared by dissolving 0.520 g of the above product in 3.65 mL methanol. The solution was then charged with 0.078 g of type 3 Cuno Zeta loose carbon and allowed to stir for 0.25 hours. The mixture was then filtered and washed with 6 ml of methanol. The product rich solution was concentrated down to 2.6 mL by vacuum distillation. 7.8 mL acetone was added and allowed to stir at 25 °C for 15 h. The solids were filtered, washed with 2.5 mL 2: 1 acetone:ethanol and dried in a vacuum oven at 70 °C to give 0.406 g (57.0%) of the desired product as white crystals: ¹H NMR (400 MHz, OMSO-d₆, 80 °C): 8.02 (d, J=8.34 Hz, 4 H), 7.97 (s, 2 H), 7.86 (d, J=8.34 Hz, 4 H), 6.75 (s, 2 H), 5.27 (t, J=6.44 Hz, 2 H), 4.17 (t, J=6.95 Hz, 2 H), 3.97 - 4.11 (m, 2 H), 3.74 - 3.90 (m, 2 H), 3.57 (s, 6 H), 2.32 - 2.46 (m, 2 H), 2.09 - 2.31 (m, 6 H), 1.91 - 2.07 (m, 2 H), 0.88 (d, J=6.57 Hz, 6 H), 0.79 (d, J=6.32 Hz, 6 H); ¹³C NMR (75 MHz, DMSO- d₆): δ 170.9, 156.9, 149.3, 139.1, 131.7, 127.1, 126.5, 125.9, 115.0, 57.9, 52.8, 51.5, 47.2, 31.1, 28.9, 24.9, 19.6, 17.7; IR (neat, cm⁻¹): 3385, 2971, 2873, 2669, 1731, 1650. Anal. Calcd for C₄₀H₅₂N₈O₆Cl₂: C, 59.18; H, 6.45; N, 13.80; Cl, 8.73. Found C, 59.98; H, 6.80; N, 13.68; Cl, 8.77. mp 267 °C (decomposed). Characteristic diffraction peak positions (degrees 2θ ± 0.1) @ RT, based on a high quality pattern collected with a diffractometer (CuKα) with a spinning capillary with 2θ calibrated with a NIST other suitable standard are as follows: 10.3, 12.4, 12.8, 13.3, 13.6, 15.5, 20.3, 21.2, 22.4, 22.7, 23.7”.

(d) It is submitted that Claims 1 to 12 of ‘806 are expressly encompassed within Claim 1 and Claim 23, when read with example 24-23, of ‘853. The Opponents submit

that although the Applicant has not specifically claimed Form N-2 of Compound (I) in '853, it is nevertheless disclosed in the application. The invention claimed in '806 forms the subject matter of the earlier application '853. Therefore, while not having specifically filed a claim for the said compound in '853, the Applicant should not be permitted to claim the same compound in a different patent application and extend its monopoly rights.

(e) In view of the above, the Claims of '853 amount to prior claiming of the subject matter covered in Claims 1 to 12 of '806. Even though Form N2 and its pharmaceutical composition as claimed in '806 are not specifically claimed in '853, the Opponents contend that they are encompassed within the claims of '853 given its broad claims to "*daclatasivir or a pharmaceutical salt thereof*". Indeed, this is made apparent by the disclosure the crystalline form in '853 on pages 157-159, Example 24-23.

(f) If the Applicant is allowed to patent Claims 1 to 12 of '806 despite the claims and disclosures in the earlier filed application of '853, it would unfairly allow the Applicant to extend its exclusivity over the said subject matter. As such, Claims 1 to 12 should be rejected under Section 25(1)(c).

5.2 GROUND II

Claims 1 to 12 of '806 are obvious, do not involve a technical advance, lack inventive step as defined Section 2(1)(j) and 2(1)(ja) and, therefore, should be rejected under Section 25(1) (e) of the Act

5.2.1 Section 2(1) (j) defines an "invention" as a new product or process involving an *inventive step* and capable of industrial application. Therefore, all alleged inventions, in order to qualify for a patent, must satisfy the criteria of inventive step.

5.2.2 Section 2(1) (ja) of the Patents Act defines an inventive step as "a feature of an invention that involves technical advance as compared to the existing knowledge or having economic significance or both and that makes the invention not obvious to a person skilled in the art. These requirements are laid down to ensure that patents, which result in a monopoly, are granted only to genuine inventions. The requirement of inventive step, as defined in Section 2(1) (ja) encompasses two requirements:

- first, the feature involved in the alleged invention ought to involve a technical advance as compared to the existing knowledge; and
- second, the feature should not be obvious to the person skilled in the art.

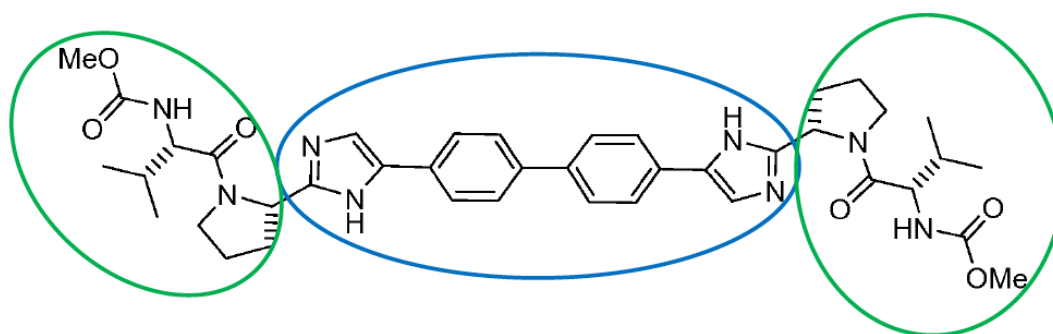
5.2.3 In the alternative and without prejudice to the grounds raised above, Claims 1 to 12 of '806 do not amount to a technical advance over prior published matter and existing knowledge in the field. As such, Claims 1 to 12 lack inventive step and would have been obvious to one skilled in the art.

5.2.4 The Opponents' arguments under Section 25(1)(e) may be summarised as follows:

- The base compound of daclatasvir as found in '806 is obvious in light of a combination of the prior arts D2, D3 and D4; or
- In the alternative, the base compound as found in '806 is obvious in light of a combination of the prior arts D5 and D4, supported by D6 and D7; and
- The selection of the dihydrochloride salt and crystallizing of the compound daclatasvir to obtain the Form N-2 compound claimed in '806 is nothing more than a routine exercise that requires no inventive step for a person skilled in the art.

5.2.5 The following paragraphs set out the Opponents' arguments and supporting prior art in more detail:

Daclatasvir, a HCV NS5A replication complex inhibitor, is represented by the following formula:



This compound is also known as BMS-7900052 or methyl(((1S)-1((((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyllyl)-1H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate.

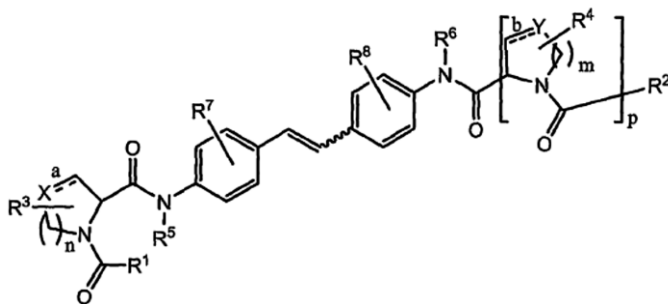
Daclatasvir presents a symmetrical structure with a central rigid core containing a biphenyl-imidazole (circled in blue), which serves as a linker to two peptide-like side chains (circled in green).

A) Combination of D2, D3 and D4

The base compound claimed in '806 is obvious in light of a combination of the prior arts D2, D3 and D4 as set below:

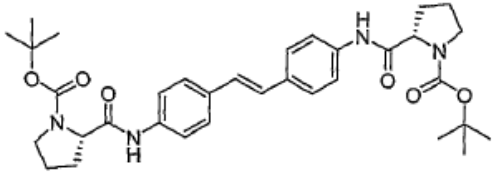
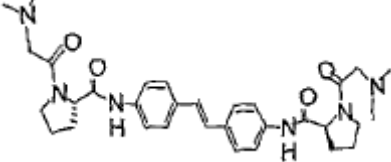
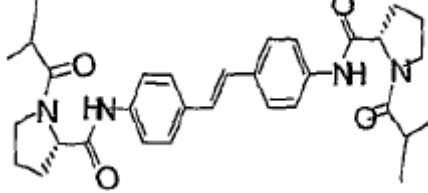
5.2.6 WO2006/133326A1 (WO '326) titled "Inhibitors of HCV replication", Bristol-Myers Squibb company, published December 14, 2006, marked as D2.

(a) **D2** relates to a compound of formula I (see pages 3 and 4) that can inhibit the HCV replication, in particular the function of the HCV NS5A protein. D2 discloses pyrrolidine compounds:



(b) The compound of formula (I) disclosed in D2 resembles the base compound daclatasvir in '806, in that it provides substituted pyrrolidine moieties attached to phenyl rings in a symmetrical arrangement and also possess HCV inhibitory activity. D2 also discloses groups similar to the end group substitutions such as alkoxy carbamate on the pyrrolidine rings.

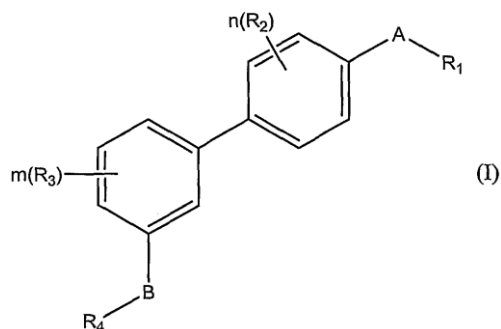
(c) The exemplary compounds disclosed in D2 include the following:

Page 38	
Example 28, page 43	
Example 39, page 44	

(d) These examples and other disclosures in D2 provide the same absolute stereochemistry of the pyrrolidine rings as found in '806. Moreover, D2 provides biological activity of the compounds disclosed therein using a HCV replicon assay. Therefore, it is evident that the compounds bearing substituted pyrrolidine moieties attached to phenyl rings in a symmetrical arrangement possess HCV inhibitory activity. A person skilled in the art could conclude from D2 that the class of substituted pyrrolidine moieties are suitable as agents to treat HCV. The Opponents state that the Markush structures of D2 and the compound claimed in '806 have strong similarities. Accordingly, a person skilled in the art would be motivated to use D2 as a basis for developing an alternative HCV compound such as that claimed in '806. In view of D2, the proposed compound of '806 is an obvious solution to the problem of providing further HCV agents.

5.2.7 WO2007/031791A1 (WO '791) titled "Biphenyl derivatives and their use in treatment of hepatitis, Arrow Therapeutics Limited, published March 22, 2007 marked as D3.

D3 relates to a series of biphenyl derivatives, which are useful in treating or preventing a HCV. D3 on pages 1 and 2 provides a compound, which is a biphenyl derivative of formula (I), or a pharmaceutically acceptable salt thereof:

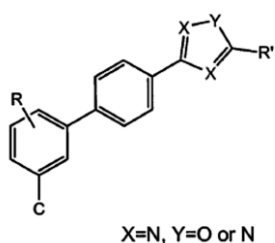


Wherein $R_1 = A_1\text{-Het}_1\text{-Y}_1\text{-A}_1, A_1\text{-Het}_1\text{-L}_1\text{-A}_1$;

A and B are the same or different $\text{-CO-NR}'$;

R_4 is $\text{-CO-O-(C}_1\text{-C}_4\text{ alkyl)-NR}'\text{R}''$

The relevant generic compound disclosed above is provided on page 48:

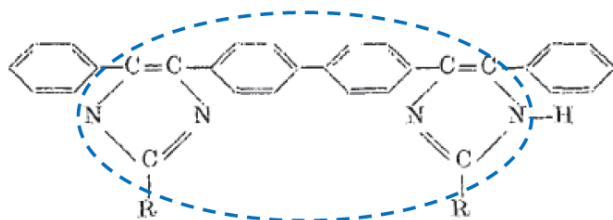


Moreover, pages 149 to 153 of D3 also provides both the IC₅₀ and the TD₅₀, the concentration of drug required to reduce the total cell area by 50% relative to the DMSO controls on page 149 to 153.

Therefore, it is apparent from D3 the importance of a biphenyl moiety as an active HCV inhibitor. It also teaches the importance of attaching to the biphenyl moiety a substituted heterocyclic ring that may optionally be an imidazole. The Opponents submit that with the structural and functional similarities there is clear motivation for the person skilled in the art to derive the structure of the compound claimed in '806 from the teachings of D2 combined with D3.

5.2.8 Hermann. S et al., "Synthesis of aromatic-linked 4(5), 4'(5')-diimidazoles, Journal of Practical Chemistry, 4 series, Volume 22, published 1963, marked as D4.

D4 as shown below (see page 3 of the English translation and page 143 of the original German version of the article) describes the synthesis of aromatic bridge compounds, in particular the symmetric structural arrangement of the biphenyl-imidazole:



D4 clearly shows that it is known that a biphenyl imidazole containing symmetric compounds were known. The Opponents state that the Markush structures of D4 and '806 have similarities in the basic biphenyl imidazole ring.

5.2.9 Accordingly, in view of the combination of D2, D3 and D4, it would have been obvious for a person of ordinary skill in the art to arrive at a compound which contains:

- a symmetrical structure;
- a biphenyl ring structure;
- two terminal substituted pyrrolidine rings;
- an imidazole moiety attached to the phenyl rings:
- the arrangement of the biphenyl ring structure and also the substitutions on -either side of the molecule as -A1-Het1-Y1-A1' or --A1-Het1-L1-A1', which is -imidazole-pyrrolidinyl-carbonyl-(heterocycle, or carbocycle); and
- the structural arrangement of the biphenyl and the imidazole moieties; and
- to contain an alkoxy carbamate substituent at the terminal pyrrolidine rings.

The Opponents submit that from the disclosures provided in D2, D3 and D4, it is possible to arrive at one phenyl ring connected to an imidazole ring, which is further connected to a pyrrolidine nucleus to obtain the basic structural skeleton of the compound found in '806.

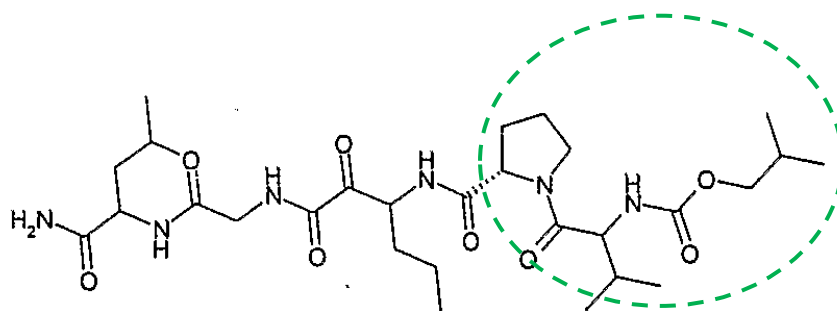
B) Combination of D5 and D4, Supported by D6 and D7

In the alternative and without prejudice to the arguments made above, a combination of the references D5 and D4 (supported by D6 and D7) would have made it obvious to one skilled in the art to arrive at the compound daclatasvir.

5.2.10 WO 03/062265 titled “Novel peptides as NS3 serine protease inhibitors of Hepatitis C virus” Published on July 31, 2003, Schering Corporation and Corvas International Inc marked as D5.

(a) **D5** discloses novel compounds which have HCV protease inhibitory activity as well as methods for preparing such compounds.

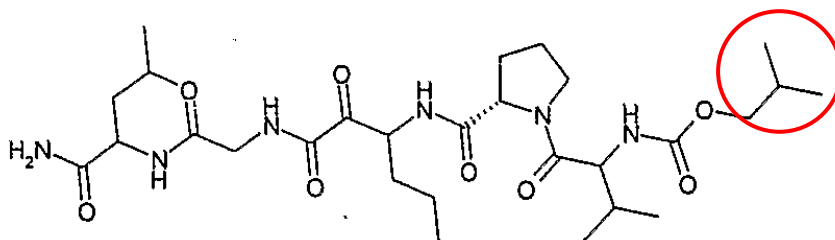
(b) D5 in particular discloses the following compound on page 135:



(c) The Opponents submit that the compound above presents a resemblance with daclatasvir, as the part circled in green (pyrrolidine alkylglycine moiety) is similar to the peptide-type side chains of daclatasvir except for the terminal butyl, which is replaced by a methyl in daclatasvir. This compound is an anti-HCV compound, which presents an inhibitory action against HCV NS3 protease (K_i category C > 1000 nM) (see pages 47 & pages 135).

(d) In this regard, it should be noted that according to Exhibit 3 (WO ‘927), which claims the base compound of daclatasvir, the compounds described therein may inhibit HCV by mechanisms **in addition to or other than N5SA inhibition** (see page 627 of Exhibit 3, lines 19-22). Accordingly, it is justified to select a NS3-inhibitor as a suitable reference as a starting point for the purpose of making the argument that the compound in ‘806 is obvious and lacks inventive step.

(e) D5 provides that the butyl substituent (circled in red below) of the carbamate group (-NH-C(=O)-O-) of the closest prior art compound on page 135 could be a methyl (see pages 7-9 and pages 35-36).



(f) It is well known to a person skilled in the art that the methyl group can be used as a carbamate protecting group.

(g) Accordingly, it would have obvious to a person skilled in the art to substitute the terminal butyl group of the above compound by a methyl. In other words, selecting a methyl carbamate instead of an isobutyl carbamate results from an arbitrary choice between known functional equivalents, which consequently does not involve an inventive step.

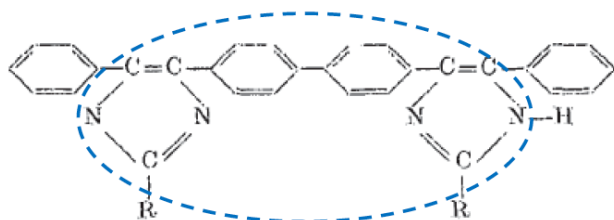
(h) Indeed, it was common technical knowledge at the priority date of '806, as illustrated by D6 below, that it was advantageous to impart NS3-inhibitors with a certain structural rigidity.

5.2.11 Chao Lin, HCV NS3-4A Serine Protease, Hepatitis C Viruses Genomes and Molecular Biology, *Horizon Bioscience*, Seng-Lai Tan, published 2006 marked as D6.

(a) The Opponents submit that **D6** essentially focuses on the discovery and clinical development of HCV NS3-4A protease inhibitors as novel antiviral therapies. It specifically teaches that significant enhancement in potency was achieved with the addition of large, hydrophobic aromatic rings to the P2 Pro group, resulting in potent tetra-peptide inhibitors (Goudreau et al., 2004b). D6 also discloses that a macrocyclic

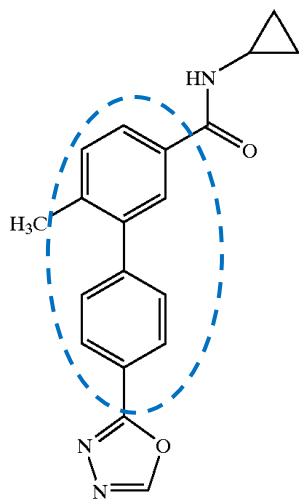
ring was designed to link the side chain of the P1 and P3 residues to reduce the peptidic nature and provide rigidity to pre-order the binding conformation (Tsantrizos et al., 2003). The article also discloses that the rigidity imparted by the ring structure constricts the molecule into exclusively adopting the correct rotamer for binding to the backbone of the NS3 protease.

(b) Therefore, one skilled in the art looking for an alternative anti-HCV compound to that disclosed in D5 would have been prompted to impart rigidity to the said compound and would, therefore, have considered D4. As already highlighted above in paragraph 5.2.8, the authors of this article describe the synthesis of aromatic bridge compounds, in particular biphenyl-imidazole (see below), which is reported by the authors to represent a very inflexible compound:

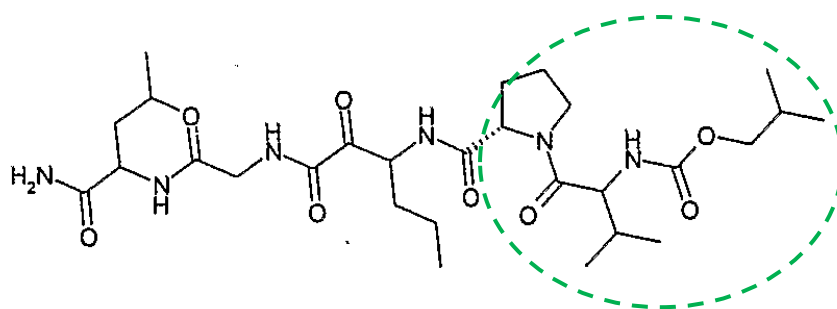


5.2.12 US 2005/0020590 (US ‘590) titled “P-38 Kinase inhibitors” published on January 27,2005, marked as D7.

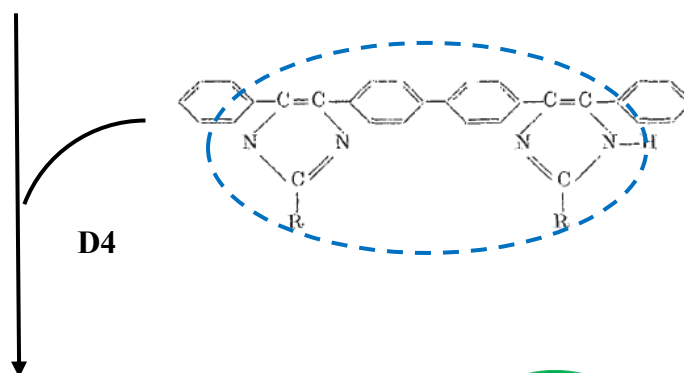
‘590 discloses compounds and compositions for modulating the activity of p38 kinases. The disclosures provided in **D7** are significant in that biphenyl compounds are revealed. The incentive to turn to biphenyl compounds would have also have been reinforced by **D7**, which describes that compounds such as the following compound of Example 1 (see paragraph [0209] on page 16) are useful to treat hepatitis C (see paragraph [0155] on page 15):



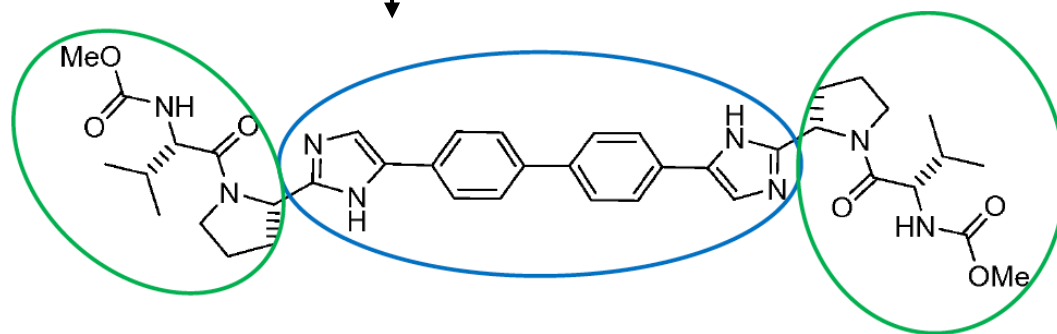
The arguments made above may be summarised as follows:



D5



D4



Daclatasvir

Accordingly, it would have been obvious to one skilled in the art to append two prolyl-valyl-carbamate-like moieties of the compound in D5 (i.e. the peptide-type side chain circled in green), in which the terminal butyl has been substituted by a methyl, to a rigid biphenyl-imidazole central core, in order to yield an alternative anti-HCV compound. As such the base compound of daclatasvir does not involve inventive step.

C) Selection of the Dihydrochloride Salt and Crystallizing of the Compound Daclatasvir.

(a) Having established the lack of inventive step for the basic compound that is daclatasvir, the Applicant asserts in '806 that due to the difficulty of crystallizing the compound "methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl)amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1H-imidazol-5-yl)-4-biphenyl)-1H-imidazol-2-yl)-1-pyrrolidinyl) carbonyl)-2-methylpropyl) carbamate it has discovered the dihydrochloride salt of daclatasvir in order to crystallize the same. The Applicant claims that the dihydrochloride salt can be repeatedly crystallized into one particular polymorph – Form N-2 and offers high aqueous solubility and excellent purification capacity. The Opponents submit that once a compound has been made, preparing various salts of it and checking for polymorphs is a routine exercise in the course of drug development.

(b) The Opponents contend that given the existing common general knowledge in the field, salt selection for a compound and checking for its polymorphs is routine practice for one skilled in the art. A person skilled in the art would have known that any acidic or basic moiety on a drug molecule, such as daclatasvir, may be converted into a salt by an acid-base reaction. It would also be known that basic amines that possess a lone pair of electrons are very often converted into salts by reaction with a corresponding acid and that the 'salt form' of a drug is nearly always more crystalline and more water-soluble than the base form of the molecule. As a result, the properties of crystallinity and water solubility imparted by salt formation are commonly practiced in the field for dissolution and absorption upon human dosing and for the ease of formulation during drug development and manufacturing.

(c) To substantiate the above, the Opponents rely on the following prior art to show that the claimed invention in '806, namely the dihydrochloride salt of daclatasvir, which

can be repeatedly crystallized into one particular polymorph – Form N-2, does not amount to a technical advance and, therefore, lacks inventive step.

5.2.13 Gould, P.L., “Salt selection for basic drugs”, *International Journal of Pharmaceutics*, vol. 33, pp 207-217, published 1986, marked as D8

(a) With respect to the Applicant’s claim of obtaining the dihydrochloride salt, the Opponents rely upon **D8** to show why such a step is routine practice and would have been obvious. D8 sets out the decision process for salt selection and how to achieve the desired properties. D8 also provides a list of the most commonly approved salts for commercial purposes as approved by the U.S Food and Drug Administration (U.S. FDA). It is noticeable from D8 that hydrochloride and dihydrochloride salts of drugs have frequently been approved by various regulatory agencies worldwide. Indeed, it is stated on page 202 of D8 that of the total approved salts, hydrochloride constituted 42.98% and dihydrochloride 0.51%.

(b) Therefore, D8 establishes that there are a limited number of salts that are used for commercial purposes, with hydrochloride and dihydrochloride salts being commonly used. It must also be noted that the difference between choosing a hydrochloride versus a dihydrochloride salt for development is not an inventive exercise. Molecules that have more than one basic nitrogen have more than one site available for protonation. As such, the selection of a dihydrochloride salt versus a mono-hydrochloride is a reflection of the structure of daclatasvir (or a similar drug molecule) itself, rather than any inherent inventive concept in the choice of a dihydrochloride salt.

5.2.14 Bighley. L et al., "Encyclopaedia of Pharmaceutical Technology", vol. 13, pages: 453 – 499, published 1995, marked as D9.

(a) **D9** discloses potential useful salts and their effect on the properties of the parent drug. The article also describes a decision tree for choosing the most desirable salt form (s) of the compound.

(b) On page 456, D9 discloses that “*It is well documented that due to differences in physical, chemical and thermodynamic properties imparted by the salt-forming species,*

various salts of the same compound often behave differently. Knowledge that a particular salt form imparts enhanced water solubility, reduced toxicity or slow dissolution rate to a drug molecule benefits chemists and formulators.

(c) Bearing that in mind, and given that a person skilled in the art would be able to narrow the salts suitable for selection based on the respective properties of the base compound and salt, as discussed in D9, it would have been obvious for the Applicant to select the dihydrochloride salt for the purpose intended in '806.

5.2.15 Guillory, J. K., "Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids," Chapter 5 in Polymorphism in Pharmaceutical Solids, Brittain, H. G., Ed., vol. 95 of Drugs and the Pharmaceutical Sciences, Marcel Dekker, Inc., New York, NY, 1999, pp. 183-226., Published 1999, marked as D10.

(a) As with salt selection, obtaining a polymorphic form is a routine exercise for a person skilled in the art. It is well known that organic compounds exhibit polymorphism and most of the compounds can exist in more than one polymorphic form including their different salt forms (see **D10**, pages 184-186).

(b) A polymorph screen is a routine pre-formulation step, which involves crystallizing an active pharmaceutical ingredient (API) from a variety of solvents and solvent mixtures and characterizing the resulting crystals for evidence of polymorphism or pseudopolymorphism. It is common general knowledge and practice at the time of filing a patent to carry out a polymorph screen in respect of an API to be commercially marketed.

5.2.16 International Conference on Harmonisation: Guidance on Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances, Federal Register, Vol 65, No. 251, published December 29, 2000, marked as D11.

(a) **D11**, a guidance document by the Food and Drug Administration (FDA), provides recommendations about the selection of test procedures and the acceptance criteria for new chemical drug substances and new drug products. **D11** discusses polymorphism in

drug substances and teaches that new drug substances exist in different crystalline forms, which result in different physical properties. The guidance document also provides how differences in the polymorphic forms can affect the quality and or performance of new drug products. D11 also discusses the various procedures, such as melting point (including hot-stage microscopy), solid state IR, X-ray powder diffraction, thermal analysis procedures (like DSC (differential scanning calorimetry), TGA (thermogravimetric analysis) and DTA (differential thermal analysis)), Raman spectroscopy, optical microscopy, and solid state NMR (nuclear magnetic resonance) spectroscopy, that are used for the detection of the different polymorphic compounds.

(b) D11 teaches that the preparation of polymorphs is an important approach to modify the physical and chemical properties of the concerned product. Therefore, D11 provides the necessary guidance to a person skilled in the art to obtain polymorphic forms as claimed in '806. As a result, Claims 1 to 12 of '806 are obvious to a person skilled in the art and do not involve any technical advance over the existing knowledge

5.2.17 Byrn, S., et al., “Pharmaceutical Solids: A Strategic Approach to Regulatory Considerations”, *Pharmaceutical Research*, col. 12, no. 7, pp. 945-954 (Published 1995), marked as D12.

(a) Bryn *et al* discusses the importance of controlling the crystalline form of drug substances in the New Drug Application (NDA) and Investigational New Drug (IND) process. **D12** outlines the investigations and analytical tests available for identifying various polymorphic forms and controls needed to ensure the integrity of drug substance containing either a single morphic form or a mixture. The decision tree provided in D12 also suggests various solvents that are commonly used in recrystallization, including water methanol, ethanol, propanol, isopropanol, acetone, acetonitrile, ethyl acetate, hexanes and mixtures if appropriate.

(b) D12 provides that it is advisable to investigate the drug substance for the existence of polymorphs and hydrates since these may be encountered at any stage of the drug manufacturing process or upon storage of the drug substance or dosage form. As a result, given that recrystallization purification purposes is well known in the art, it should not be considered a surprising element.

(c) The Opponents submit that once a product or chemical substance is known, crystallization of the substance merely involves routine trial and error to achieve different polymorphic forms. A common general process for purifying and crystallizing an organic compound involves first dissolving the crude compound in a suitable solvent or a mixture of solvents, filtering the hot solution, allowing the hot solution to cool, which causes the dissolved compound to crystallize out and separating the crystals further while drying.

(d) As set out above in D11 and D12, every new compound that is entered into human clinical trials in the US or Europe undergoes a fairly routine series of experiments (Polymorph Screen) before an original INDA (Investigational New Drug Application) is filed with a strict regulatory authority. This includes allowing the slow evaporation of solutions of the drug substance from many different solvents and/or solvent mixtures of differing properties (e.g., polarity, dielectric constant, boiling point) to encourage the crystallization of different polymorphs, solvates, or hydrates. These studies are a routine part of the preclinical development program for API characterization and pre-formulation. Regulatory Authorities require a demonstration of consistency or “similarity” in the batch-to-batch performance of APIs and formulations as part of beginning human clinical trials. Stability, dissolution, absorption, and bioequivalence are dependent upon this consistency in physicochemical properties. For this reason, all new drug candidates in the E.U and the U.S undergo such screening as a routine exercise before first-in-human studies.

(e) In view of the above prior art, the Applicant’s claims for finding the dihydrochloride salt of daclatasvir, which can be repeatedly crystallized into one particular polymorph – Form N-2 and offers high aqueous solubility and excellent purification capacity, is nothing more than routine practice for a person skilled in the art of drug development. As a result Claims 1 to 12 of ‘806 provide no technical advance over the known art and, therefore, would have been obvious to a person skilled in the art. Accordingly, ‘806 should be rejected on the grounds of lacking inventive step.

5.3 GROUND III

Claims 1 to 12 are not an invention within the meaning of this Act and should be rejected under Section 25 (1) (f) of the Patents Act read with Section 3(d).

5.3.1 The Hon'ble Supreme Court in *Novartis AG vs Union of India & Others (AIR 2013 SC 1311)* (hereinafter the "Glivec case"), observed "[T]he amended portion of Section 3(d) clearly sets up a second tier of qualifying standards for chemical substances/pharmaceutical products in order to leave the door open for true and genuine inventions but, at the same time, to check any attempt at repetitive patenting or extension of the patent term on spurious grounds".

[See page 56, para 103].

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

[See page 90, para 180].

The Court also stated that:

"...the physico-chemical properties of beta crystalline form of Imatinib Mesylate, namely (i) more beneficial flow properties, (ii) better thermodynamic stability, and (iii) lower hygroscopicity, may be otherwise beneficial but these properties cannot even be taken into account for the purpose of the test of section 3(d) of the Act, since these properties have nothing to do with therapeutic efficacy"

[See Glivec case, page 94, para 187]

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

[See Brunton L.L, Lazo J.G et al, "Goodman and Gilman's The Pharmacological Basis of Therapeutics" 11th edition, McGraw-Hill, Page 35, lines 1-7 (hereinafter Goodman et al.), filed herewith as **D13**].

5.3.3 Another useful and more detailed definition of efficacy is that provided in Tripathi K.D, “Essentials of Medical Pharmacology, 5th edition, Jaypee Brothers Medical Publishers Ltd, Page 37, lines 10-13 (hereinafter Tripathi et al.), (filed herewith as **D14**) which broadly defines efficacy as “*ability of the drug to activate (induce a conformational change in) the receptor consequent to receptor occupation.*”

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

5.3.4 The claimed subject matter of ‘806 falls under Section 3(d) as it is a new form of a known substance. The Opponents submit that the alleged invention in ‘806 forms the subject matter of the earlier patent application ‘853. It is, therefore, incumbent upon the Applicant to show the Claims of ‘806 result in the enhancement of therapeutic efficacy over the known forms discussed above. The Applicant has failed to meet this obligation as no data is provided in the application demonstrating any enhancement in the therapeutic efficacy of crystalline Form N-2 of daclatasvir over the base compound disclosed in ‘853. The only claim the Applicant makes in ‘806 is that Form N-2 offers high aqueous solubility and excellent purification capacity. However, as has been confirmed in *Novartis AG v. Union of India* 2013 (54) PTC 1 (SC), physico-chemical properties such as solubility are not sufficient to fulfil the requirement of therapeutic efficacy as mandated by Section 3(d) of the Act. The Opponents further submit that there is no example or any disclosure in the complete specification which would support any assertion of enhanced stability.

It is submitted that in the absence of any evidence of an enhancement of efficacy, Form N-2 as claimed in Claims 1 to 12 should be rejected under Section 3(d).

5.4 GROUND IV

The complete specification does not sufficiently and clearly describe the invention as claimed in Claims 1 to 12 and should be rejected under 25 (1) (g) of the Patents Act.

5.4.1 Section 25 (1) (g) of the Patents Act provides a ground for opposition if the complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed.

Section 10(4) of the Patents Act requires the complete specification to fully and particularly describe the inventions and its operation or use.

5.4.2 Without prejudice to the other grounds raised above, the complete specification does not sufficiently and clearly describe all the Claims in '806.

At the outset, the Opponents state that the entire rationale of the patent system is a *quid pro quo*, whereby the Patent Office grants a patent to an inventor when s/he discloses the mode and method of performing an invention. This is done for two reasons; one to gauge the patentability of the subject invention and the other to enable an unimaginative individual having sufficient skill in the art, to perform the invention in its best embodiment. The Opponents submit that a complete specification should sufficiently and clearly describe the invention and not leave a person skilled in the art in a state where he has to perform undue experimentation to perform the invention.

5.4.3 The currently amended claims for '806 describe Form N2 characterized by one or more of a) unit cell parameters b) X-ray diffraction (XRD) and/or c) differential scanning calorimetry (DSC). However, on pages 3, 4 and 5 of '806, the only support for determining XRD is based on a "high quality pattern with a diffractometer (CuK α) with a spinning capillary with 2 θ calibrated with a NIST other suitable standard."

5.4.4 The Claims as filed for '806 do not include the restriction provided in the description of the patent for measuring XRD. As a result there is no support for the crystalline form that could have the same unit cell parameters and DSC. Indeed, the XRD could be different from the claimed form by virtue of using a different measurement system, which does not have a spinning capillary and/or is not calibrated with a NIST or

an equivalent standard. Sample spinning is an option that may be opted for and it not necessarily present in every XRD measurement.

5.4.5 A capillary geometry with spinning possibility is an option and not an integral part of all XRD instruments. In particular, many diffractometer designs do not permit the sample to be rotated. Even within the spinning option, capillary samples may be rotated about the capillary axis and there are also flat-plate sample holding options that can be rotated about an axis normal to the flat plate. With a capillary sample, spinning changes the orientation of the individual grains in the powder sample, with the result that more crystals will satisfy the Bragg condition some of the time. Since the capillary is fully bathed by the X-ray beam, the number of particles irradiated is unchanged by spinning.

By contrast, with a flat-plate sample, only part of the sample is illuminated by the beam such that the effect of rotation is to change not only the orientation of the grains, but to irradiate more of the sample. As a result, this could result in different readings. Therefore, the instrument specification that is provided in the description of '806 for measuring the XRD and its collaboration with other parameters like unit cell measurements and DSC is very specific with a certain design configuration and hence may not support the XRD obtained using instruments of different designs and configurations.

5.4.6 It should also be noted that the National Institute of Standards and Technology (NIST) certify a variety of Standard Reference Materials (SRMs) to address specific aspects of instrument performance for divergent beam diffractometer. In the absence of any information regarding the specific standard that has to be employed for determining the XRD data, it is difficult for a person skilled in the art to record XRD data using only the information on spinning capillary with 2θ .

In view of the above, the Applicant has failed to sufficiently and clearly describe the invention and the Claims of '806 are invalid under Section 25(1) (g) for this reason.

In addition to the above, the Applicant has failed to provide any comparative data in '806 in terms of product property, stability and performance to prove that the crystalline form N-2 claimed is actually different from the already disclosed product described Exhibit 3.

In view of this omission, the Applicant has not fulfilled the requirement of sufficiently describing the invention claimed for which protection is sought. Accordingly, '806 should be rejected under Section 25 (1) (g).

5.5 GROUND V

The Patent Applicant has not complied with the requirements of Section 8. Therefore, the Claims 1 to 12 are not patentable under Sections 25(1)(h) of the Act.

5.5.1 Section 25 (1) (h) of the Patents Act provides a ground for opposition if the Applicant has not furnished information required under Section 8 of the Patents Act, within the time prescribed by law.

Without prejudice to the grounds raised above, the present application '806 should be rejected because the Applicant has not complied with the mandatory requirements of Section 8 of the Act.

5.5.2 Section 8 read with Rule 12(1) requires the Applicant, who is prosecuting, either alone or jointly with any other person to file a statement at the Indian Patent Office at regular time intervals stating whether he/she has made any application for a patent for the same or substantially same invention in any foreign country or countries and to furnish particulars of any such applications - especially objections raised and the amendments to the specifications.

Failure to disclose this information is a ground for opposing the grant of a patent under Section 25(1) (h) of the Act. Therefore, the burden is on the Applicant to furnish any and all foreign search reports from "any country outside India" in its possession at the time of its reply to the patent office.

5.5.3 Based on the requirement of Section 8 of the Act, '806 should be rejected on the grounds that the Applicant has failed to disclose that it filed a continuation application, US 13/176,970 (published as US 20110268697 and attached as **Exhibit 4**), which has now been abandoned. US 13/176,970 claims Form N-2 of daclatasvir as claimed in '806. However, unlike '806, US 13/176,970 is based on the earlier patent '927 (see Exhibit 3)

and claims a different priority claim of 11 August 2006, whereas ‘806 has a priority claim of 8 August 2007.

The Opponents submit that Applicant in their Form 3 submissions dated February 05,2010, May 17,2010 and October 21, 2015, attached herewith as **Exhibit 5** have deliberately concealed this material information from the Patent Office. At the time of submitting this opposition it is noticeable from the last Form 3 information submitted by the Applicant on 21 October 2015, it does not contain any information relating to US 13/176,970 (published as US 20110268697 – Exhibit 4). Indeed, the most recent Form 3 makes no mention of corresponding filings in the U.S.

It is further submitted that the Applicant has failed to comply with the requirements of Section 8(2) despite the Patent Office specifically requesting this information in the First Office Action dated October 29, 2014. The corresponding EP and US applications were examined some time ago. The Applicant has failed to file these documents within time and on this ground alone the application should be refused.

In view of the above, the Applicant appears to have failed to meet its obligations under section 8. Accordingly, under Section 25(1)(h), the failure of the Applicant to disclose information as required under Section 8, or furnish information which in any material particular was false to his knowledge is a ground to reject the patent application.

5.6 GROUND V:

The Patent application ‘806 was not filed within 12 months from the date of the first application for the invention made in a Convention country by the Applicant. Claims 1 to 12 of ‘806 are not patentable under Section 25(1)(i) of the Act

5.6.1 ‘806 is not patentable under Section 25(1)(i) because the convention application was not filed in India within twelve months from the date of the national application from which the priority is claimed. The Applicant was in possession of the dihydrochloride salt and specific crystalline Form N-2 of daclatasvir before the priority date of the instant application, and has tried to claim the same within the another patent family as evidenced by the following filings.

5.6.2 Published application EP2385048A1 (EP '048) (attached as **Exhibit 6**) was filed on August 09, 2007 and claimed priority from an application filed August 11, 2006. EP '048 was later withdrawn on 22 June 2012. EP2385048A1 sought to claim dihydrochloride salts specifically within the same priority of August 11, 2006. However, the application was rejected by the European Patent Office (EPO) on the grounds of potential double patenting as set in **Exhibit 7**.

5.6.3 Published application EP2784075B1 (attached as **Exhibit 8**) was also filed on August 9, 2007 and claimed priority from an application filed on August 11, 2006. Claim 2 of this patent specifically claims the dihydrochloride of methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl) amino)-3-methylbutanoyl)-2-pyrrolidinyl)-1 H-imidazol-5-yl)-4-biphenyl)-1 H-imidazol-2-yl)-1-pyrrolidinyl)carbonyl)-2-methylpropyl)carbamate and also discloses crystalline forms. The EPO found, as highlighted below and set out in **Exhibit 9**, that the specifically claimed compound in its dihydrochloride form had direct support from the PCT application WO '927, (Exhibit 3):

“The specific compound of the present claims was disclosed as "Example 24-23" in the originally filed PCT application giving rise to the said parent application. PCT claim 21 listed this specific compound and PCT claim 22 specified the compound as its dihydrochloride salt. The specific compound and its dihydrochloride salt are therefore unambiguously and directly derivable from the originally filed application. The now claims medical use is explicitly disclosed in the original claims and the description for the general class of compounds to which the now selected products belong. Since these products had originally been presented as embodiments of the said compound class also the medical use of the current claims are unambiguously and directly derivable from the application originally filed. Consequently the present claims 1-14 meet the requirement of Art. 123(2) EPC and Art. 76(1) EPC”.

5.6.4 As already stated above, the Applicant filed a continuation application US 13/176, 970, published as US 20110268697 (Exhibit 4) deriving from '927 (Exhibit 3) specifically claiming Form N2 as claimed in '806, but claiming priority from August 11,

2006 instead of August 8, 2007. US 20110268697A1 was expressly abandoned on June 19, 2012.

5.6.5 As demonstrated above, it is clear that the crystalline form claimed in '806 was subject of an application filed on August 11, 2006. In view of this, the Applicant has failed to file '806 (with a filing date of July 31, 2008) within one year from August 11, 2006. Accordingly, '806 should be rejected under section 25(1)(i).

Relief Sought:

In light of the grounds stated and the evidence presented above, the Opponents pray:

a) That Indian Patent Application No. 806/DELNP/2010 in the name of Bristol-Myers Squibb be rejected under Section 25(1) of the Patents (Amendment) Act,2005;

And in doing so

b) The Opponents be allowed to make further submissions in the event the Applicant makes any amendments to its claims;

c) The Opponents be permitted to file further evidence if necessary to support its case;

d) The Opponents be granted an opportunity of being heard in the matter before any final orders are passed.

Dated 10 day of February 2017,



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