July 21, 2023

To

The Controller of Patents,

The Patent Office,

Delhi

Re: Representation u/s 25(1) of the Patents Act – By DR. C. MANIVANNAN against
Indian Patent Application No. **4759/DELNP/2012** filed on May 29, 2012
Applicant: ABBVIE INC.

Dear Sir,

I submit herewith a Representation/Pre-grant opposition under Section 25(1) of the Patents Act, 1970 along with Form 7A, and Annexure 1 through 9 in respect of the above-referenced subject matter.

I crave leave of the Controller to submit additional documents or evidence or if necessary to support any of the averments in the representation as may be necessitated in the proceeding.

Please take the documents on record and take necessary action. It is also requested to kindly acknowledge receipt of the documents.

Lastly, I request the Controller to grant me an opportunity of being heard before the above representation is finally decided.

Yours faithfully,

Mr. Mohammad Yunus
IN/PA/2283
(Agent for the opponent)

Encl:

1. Form 7A
2. Representation for Opposition to grant of patent
3. Annexure 1 to 9

BEFORE THE CONTROLLER OF PATENTS, THE PATENT OFFICE, DELHI

IN THE MATTER OF THE PATENTS ACT, 1970 and THE PATENTS RULES 2003.

IN THE MATTER OF a pre-grant opposition under section 25(1)

AND

IN THE MATTER OF:

Indian Patent Application No. **4759/DELNP/2012** filed on May 29, 2012 by ABBVIE INC.

AND

IN THE MATTER OF:

DR. C. MANIVANNAN
3A, Chinna Andaar Street,
Kulithalai (TK), Karur (Dt),
Tamil Nadu - 639104, India ..... OPPONENT

VS.

ABBVIE INC.
1 North Waukegan Road, North Chicago,
IL 60064, USA ..... APPLICANT

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Dated this 21 July, 2023

Mr. Mohammad Yunus

IN/PA/2283

(Agent for the opponent)

To,

The Controller of Patents,

The Patent Office, Chennai

BEFORE THE CONTROLLER OF PATENTS, THE PATENT OFFICE, DELHI

IN THE MATTER OF THE PATENTS ACT, 1970 and THE PATENTS RULES 2003.

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Tamil Nadu - 639104, India ..... OPPONENT

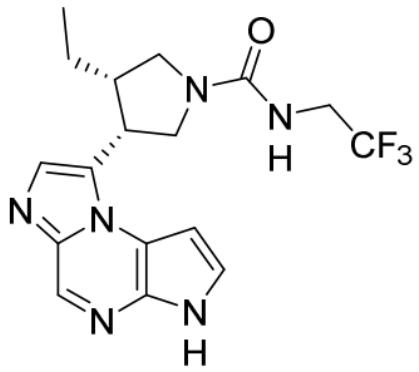
VS.

ABBVIE INC.
1 North Waukegan Road, North Chicago,
IL 60064, USA ..... APPLICANT

STATEMENT OF CASE OF OPPONENT

1. The Opponent herein is Dr. C. Manivannan of 3A, Chinna Andaar Street, Kulithalai (TK), Karur (Dt), Tamil Nadu - 639104, India. The Opponent is an individual with a Doctoral degree in Chemistry and has over 15 years of academic and research experience in the field of chemistry, life sciences and pharmaceuticals.

2. The Opponent has learnt that the Applicant has filed Indian Patent Application No. 4759/DELNP/2012 (hereinafter "the impugned application") entitled "NOVEL TRICYCLIC COMPOUNDS" and which is currently pending before the Patent Office. The impugned application was filed at the IPO on May 29, 2012 and published on Dec. 04, 2015. The impugned application originated from the international application published as WO2011068881, which in turn claimed priority from US61/265,563 of Dec. 01, 2009 and US61/364,116 of July 14, 2010. The Indian Patent Office issued First Examination Report (F.E.R.) on Sep. 27, 2017. The Applicant submitted its response to the F.E.R. on March 26, 2018 along with an amended set of 1-2 claims. The alleged invention claimed in the impugned application under opposition relates to compound represented by following structure:

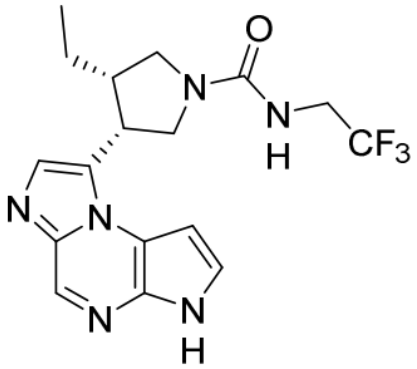


also known as "**Upadacitinib**"

or a pharmaceutically acceptable salt thereof. According to the impugned application, the claimed compound inhibits, regulates and/or modulates Jak family kinase activity that is pivotal to several mechanisms thought critical to the progression of autoimmune diseases including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), multiple sclerosis (MS), Crohn's disease, psoriasis and asthma (see, page 51, lines 14-18 of the specification of the impugned application).

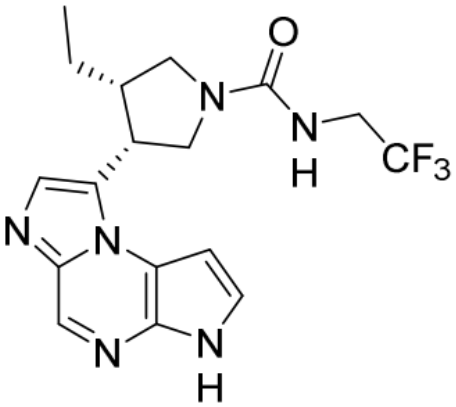
3. The Opponent by way of this present pre-grant opposition submits that the claims as currently pending and on record are not patentable under the provisions of the Patents Act. A copy of the as-filed specification of the impugned application is annexed herewith as **Annexure-1**. The claims currently on file are annexed herewith as **Annexure-2** and reproduced herein below for ready reference:

[**CLAIM 1**] A compound represented by the following structure:



or a pharmaceutically acceptable salt thereof.

[**CLAIM 2**] The compound as claimed in claim 1, represented by following structure:



4. Accordingly, the Opponent submits its opposition by way of representation under Section 25(1) in respect of said Indian Patent Application No. **4759/DELNP/2012** on the following amongst other grounds, which are without prejudice and in the alternative to each other.

PERSON SKILLED IN THE ART

5. The person skilled in the art in the present case would have had an advanced degree (Master's or Ph.D.) or equivalent experience in chemistry, pharmacology, or biochemistry, and several years' experience with the research, development, or production of pharmaceuticals.

LIST OF PRIOR ART DOCUMENTS

6. In the present opposition the following documents are referred to:

D1: WO2009152133A1 (Published Dec. 17, 2009)

D2: Flanagan et al., "Discovery of CP-690,550: A Potent and Selective Janus Kinase (JAK) Inhibitor for the Treatment of Autoimmune Diseases and Organ Transplant Rejection", J. Med. Chem. 2010, 53, pages 8468–8484. DOI: 10.1021/jm1004286 (Published Nov. 24, 2010)

D3: Jiang et al., "Examining the Chirality, Conformation and Selective Kinase Inhibition of 3-((3R,4R)-4-methyl-3-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile (CP-690,550)", J. Med. Chem. 2008, 51, Pages 8012–8018 (Published Nov. 19, 2008)

D4: Kremer et al "The Safety and Efficacy of a JAK Inhibitor in Patients with Active Rheumatoid Arthritis", ARTHRITIS & RHEUMATISM, Vol. 60, No. 7, July 2009, Pages 1895–1905. DOI 10.1002/art.24567 (Published July 2009)

D5: WO2007084557A2 (Published July 26, 2007)

D6: WO2007041130A2 (Published Apr. 12, 2007)

D7: WO2008116139A2 (Published Sep. 25, 2008)

LACK OF PRIORITY ENTITLEMENT

7. The impugned application claims two priorities. It claims the priority of US61/265,563 filed on Dec. 01, 2009 and of US61/364,116 filed on July 14, 2010. The priority document 1 (US61/265,563) does not disclose upadacitinib at all. It does not even disclose one single compound having a trifluoroethyl substituent. The priority document 2 (US61/364,116) does not disclose upadacitinib at all. While it discloses four compounds having a trifluoroethyl substituent (which is also present in upadacitinib), none of these compounds is structurally similar to upadacitinib. In consequence, the claims which relate to upadacitinib do not enjoy the priority of Dec. 01, 2009 or July 14, 2010.

8. In view of the above, we submit that the claimed priority is invalid, so that the relevant date for the assessment of patentability should be assumed to be the PCT filing date, i.e., 01 December 2010.

9. Therefore, intervening documents such as document **D1** (WO2009152133A1) become full prior art for the present claims.

GROUND I

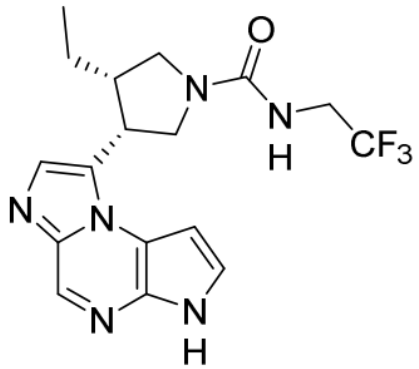
I) Section 25(1) (e): **Lack of Inventive Step: The invention so far as claimed in any claim of the complete specification is obvious and clearly does not involve any inventive step.**

10. It is submitted that the subject matter of Claims 1 and 2 of the impugned application is obvious to the person skilled in the art in light of disclosures in the prior art and clearly

does not involve any inventive step. Hence, Claims 1 and 2 ought to be rejected under Section 25(1)(e).

A. <u>Claims 1-2 lack an inventive step in view of D1, possibly further supplemented by the teachings of one or more of documents D2 to D7</u>

11. When assessing inventive step of the subject-matter of the present claims, document **D1** may be taken as the closest prior art. The claims of the impugned application are directed to a compound represented by the following formula:



also known as "**Upadacitinib**"

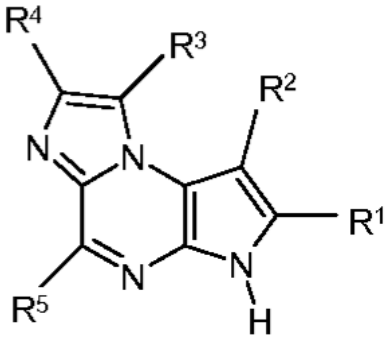
or a pharmaceutically acceptable salt thereof. According to the impugned application, the claimed compound inhibits, regulates and/or modulates Jak family kinase activity that is pivotal to several mechanisms thought critical to the progression of autoimmune diseases including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), multiple sclerosis (MS), Crohn's disease, psoriasis and asthma (see, page 51, lines 14-18 of the specification of the impugned application).

12. The Opponent states that the compounds as disclosed in **D1** and the compound as presently claimed in the impugned application (upadacitinib) have very close structural similarities and possess the same therapeutic utilities (inhibition of JAK family kinase activity). The prior art document **D1** therefore applies as the closest prior art. An unexpected effect of claimed compound over other compounds disclosed in D1 is not

apparent from the technical contents of the impugned application. Hence, starting from **D1**, the technical problem to be solved was to provide alternative compounds useful as JAK inhibitors.

13. **D1** (WO2009152133A1) discloses small-molecule compounds that inhibit, regulate and/or modulate Jak family kinase activity that is pivotal to several mechanisms thought critical to the progression of autoimmune diseases including, but not limited to, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), multiple sclerosis (MS), Crohn's disease, psoriasis and asthma (see, **D1**, page 46, lines 13-16). Thus, **D1** relates to the same therapeutic purpose as the impugned application.

14. In addition, **D1** teaches an heteroaromatic ring system that is identical to the one of upadacitinib, see e.g., claim 21 (page 371) of **D1**:



Formula (Ic)

Therefore, **D1** does not require major structural modifications in order to arrive at the compound of instant claim 1.

D1 specifies that R^1, R^2, R^4 and R^5 are each independently a hydrogen atom (see, e.g., claim 18 of D1 at page 371).

D1 specifies in its claim 13 that radical R^3 is A-D-E-G. R^3 of D1 corresponds to the substituent at position 5 of the imidazole ring in upadacitinib.

According to claim 13 of **D1**, A is a bond.

According to claim 14 of **D1**, D is a substituted pyrrolidinyl. The substituent is not defined explicitly. However, in view of the teaching of **D1** as a whole, at least C_1-C_{10} alkyl is embraced. Thus, ethyl is taught as well (compare e.g., compounds H.1.20, H.1.21, H.1.22, H.1.23 (D1, page 302) and H.1.27 (D1, page 303), H.1.35 (D1, page 304)).

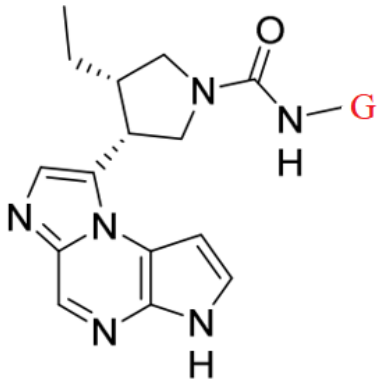
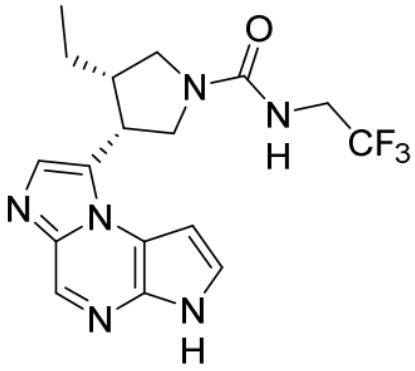
According to claim 15 of **D1**, E is R^e-C(O)N(R^a)R^e. With R^e = bond (see claim 1 of D1, page 367, line 3) and R^a = hydrogen (see claim 1 of D1, page 366, line 29), the moiety E is –C(O)N(H)–.

According to claim 16 of **D1**, G is a substituent selected from a list of cyclic structures, e.g., substituted cyclopropyl.

In summary, A-D-E-G is identical to upadacitinib except that G is not 2,2,2-trifluoroethyl.

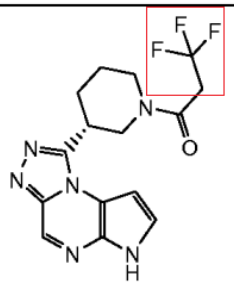
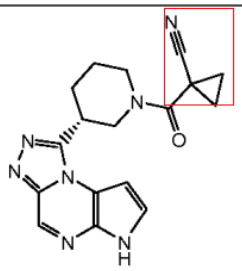
In view of this significant structural similarity and in the absence of any evidence to the contrary, it can be assumed that the pharmaceutical activity profile of compounds according to **D1** is very similar to that of upadacitinib. Thus, they are conceived for the same purpose.

15. The structure of the upadacitinib compound claimed in the impugned application is compared with the structure of the compound disclosed in **D1** in the following table:

Prior art D1	**Impugned application**
 Claim 21 of **D1** (claim 21 in combination with claims 13-16, 18 of D1)	 (**Upadacitinib**)

16. As apparent from the above comparative table, the compound upadacitinib claimed in the impugned application differs from the compound disclosed in **D1** in that a 2,2,2-trifluoroethyl radical is present instead of G. As noted above, an unexpected effect of claimed compound over other compounds disclosed in D1 is not apparent from the technical contents of the impugned application. Hence, starting from **D1**, the technical problem to be solved was to provide alternative compounds useful as JAK inhibitors. The claimed compound upadacitinib is, however, wholly obvious in view of **D1** itself. As outlined before, **D1** discloses that G is a substituent selected from a list of cyclic structures, e.g., substituted cyclopropyl (see, claim 16 of D1). A compound with this specific substituent is depicted on page 316 (L.1.3) of **D1**. Compound L.1.2 shown on the same page is identical except that the substituted cyclopropyl radical is replaced by a 2,2,2-trifluoroethyl radical. Thus, **D1** itself suggests that a substituted cyclopropyl radical is equivalent to (or at least exchangeable for) a 2,2,2-trifluoroethyl radical. Refer Excerpts:

Page 316 of D1

L.1.2	
L.1.3	

17. The Opponent therefore states that the compound upadacitinib as claimed in claims 1-2 of the impugned application is obvious in view of the disclosure of **D1** alone.

18. The specification of the impugned application describes (see, paragraph bridging pages 50 and 51 of the impugned application) that "The **Jak family kinases (Jak1 , Jak2, Jak3 and Tyk2**) are cytoplasmic tyrosine kinases that associate with membrane bound cytokine receptors……..Both Jak1 and Jak3 control signaling of the so-called common gamma chain cytokines (IL2, IL4, IL7, IL9, IL15 and IL21), hence simultaneous inhibition of either Jak1 or Jak3 could be predicted to impact Th1 mediated diseases such as **rheumatoid arthritis** via blockade of IL2, IL7 and IL15 signaling…….In summary, this **invention describes small-molecule compounds that inhibit, regulate and/or modulate Jak family kinase activity** that is pivotal to several mechanisms thought critical to the progression of autoimmune diseases including, but not limited to, **rheumatoid arthritis (RA)**, systemic lupus erythematosus (SLE), multiple sclerosis (MS), Crohn's disease, psoriasis and asthma."

19. The Opponent states that the use of JAK inhibitors for the treatment of patients with rheumatoid arthritis was well-known before the priority date of the impugned application, see, e.g., documents **D2 to D7**.

20. **D2** (Flanagan et al.) explains that the four enzymes, JAK1, JAK2, JAK3 and Tyk2, control signaling of numerous cytokines and therefore play a central role in acquired and innate immunity and hematopoiesis (see, page 8468, right column), and that blockade of the JAK1/JAK3-STAT signaling pathway with small molecules provides therapeutically desirable immunosuppression or immunomodulation, e.g., safe and effective oral treatments for rheumatoid arthritis (RA) and chronic plaque psoriasis (see, page 8469, left column, middle paragraph).

21. Similarly, **D3** (Jiang et al.) teaches that "The Jak-Stat signaling pathway is a major regulatory element for gene transcription and plays a key role in processes such as immunoregulation and cellular proliferation and differentiation. Jak3 natively associates with the common gamma chain γc forming a shared receptor for selected cytokines [including interleukin (IL)-2, IL-4, IL-7, IL9, IL-15, and IL-21]" (see, page 8013, right column, first paragraph). **D3** notes that selective JAK3 inhibitors are therapeutically useful for the treatment of rheumatoid arthritis (see, page 8012, left column, first paragraph).

22. **D4** (Kremer et al.) teaches that the orally active JAK inhibitor CP-690550 is efficacious in the treatment of rheumatoid arthritis. **D4** notes that "JAK-3 is critical for signal transduction from the common-chain of the receptors for interleukin-2 (IL2), IL-4, IL-7, IL-9, IL-15, and IL-21 on the plasma membrane to the nuclei of immune cells. These interleukins are integral to lymphocyte activation, function, and proliferation. JAK-3 is predominantly expressed in cells of the immune system.…….Therefore, agents that selectively inhibit JAK-3 have the potential to mediate potent immune modulation,

affecting T lymphocytes, B lymphocytes, macrophages, and NK cells, without significantly affecting other organ systems." (see, page 1896, left-column, middle paragraph).

23. Similar information may be gathered from documents **D5** to **D7**, which all disclose the role of Janus kinases (JAK) in cytokine signaling and the selective inhibition of JAK family kinases by heterocyclic compounds for the treatment of autoimmune diseases such as rheumatoid arthritis.

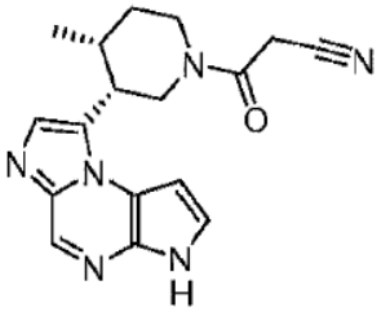
24. As indicated previously, the prior art **D1** provides clear hint leading the person skilled in the art to modify the structure of the compounds disclosed in **D1** in order to arrive at the claimed upadacitinib compound. Based on the disclosure of **D1** and possibly supplemented by the teachings of **D2** to **D7**, the person skilled in the art would have had at least a reasonable expectation of success that upadacitinib would be effective for the treatment of JAK-mediated diseases such as rheumatoid arthritis.

25. In summary, it is therefore respectfully submitted that the subject-matter of claims 1 and 2 of the impugned application is obvious and does not involve an inventive step in view of the disclosure of **D1**, possibly further supplemented by the teachings of one or more of documents **D2 to D7**.

B. <u>Lack of evidence of Inventive Step</u>

26. Generally, an inventive step is acknowledged only when an unexpected property can be assigned to the claimed subject-matter. It is accepted practice at the IPO that an unexpected property can only be demonstrated by evidence comparing the closest prior art with the claimed subject-matter and that any unexpected effect must be demonstrable across the scope of the claimed subject-matter.

27. In the present case, the Applicant's position fails at these two hurdles. There is no comparative data with the compound of the closest prior art. During the examining procedure at the EPO, the Applicant argued that example #19 (see page 277 of D1) of **D1** represented the closest prior art. The Applicant filed post-published data (IC50 values) to show that there is an effect over example #19.



Example #19 of D1

As outlined before, claim 21 of **D1** (claim 21 in combination with claims 13-16 and 18) discloses a tricyclic compound having very close structural similarity with the upadacitinib compound claimed in the impugned application. The compound of claim 21 of **D1** also has the same utility (JAK inhibitor) as the upadacitinib compound of the impugned application. Thus, it is clear that in contrast to the position taken by the Applicant, the closest prior art with respect to the upadacitinib compound of the impugned application was not Example #19 of D1, but the compound defined in claim 21 of **D1**. The position on inventive step must therefore be that the claimed upadacitinib compound must have to be compared with the compound of claim 21 of **D1**. The Applicant's data compared Example #19 of D1 and the claimed upadacitinib compound. This comparison with Example #19 cannot be considered sufficient to demonstrate the existence of a surprising effect as it is not a comparison with the closest prior art. This is a defect which cannot be fixed by post-published evidence. In such circumstances, an inventive step cannot be acknowledged for the claimed upadacitinib compound.

28. The Opponent therefore states that the impugned application ought to be rejected under this ground alone.

GROUND II

II) Section 25(1) (f): The subject-matter of the impugned application is not an invention within the meaning of this Act or is not patentable under this Act.

29. **Claims 1 and 2 are not patentable under Sections 25(f) and 3(d) of the Act**

30. The Opponent states that the claimed upadacitinib compound falls under the mischief of Section 3(d) which states: *"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"* that is not patentable.

31. As indicated previously, claim 21 of **D1** (claim 21 in combination with claims 13-16 and 18) discloses a tricyclic compound having very close structural similarity with the upadacitinib compound claimed in the impugned application. The compound of claim 21 of **D1** also has the same utility (JAK inhibitor) as the upadacitinib compound of the impugned application. As shown above, upadacitinib differs from the compound of claim 21 of D1 in that a 2,2,2-trifluoroethyl radical is present instead of G (G =

substituted cyclopropyl radical). Considering the very close structural similarities and same therapeutic utilities, it will only be fair to mention that the impugned application claims a new form (derivative) of a known substance.

32. The Opponent therefore states that the claimed upadacitinib compound can be considered as patentable u/s 3(d) only if an enhancement of known efficacy is demonstrated by the Applicant. However, the specification of the impugned application lacks any data/information demonstrating that upadacitinib results in an enhanced therapeutic efficacy over the previously known JAK inhibitors, particularly over the tricyclic compound defined in claim 21 of **D1**. It is therefore stated that the claimed upadacitinib compound is merely a derivative of the known substance of D1 without any enhanced efficacy. In absence of any enhanced therapeutic efficacy over the known compound which is structurally so close as mentioned above, the compound upadacitinib as claimed in the impugned application attracts the provision of Section 3(d) of the Patents Act, 1970.

33. In view of the aforesaid, the Opponent states that the impugned application is liable to be rejected on this ground alone.

GROUND III

III) 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.

34. **Claim 1 is not enabled**: The claim 1 covers upadacitinib as well as pharmaceutically acceptable salt thereof. But, the specification of the impugned application, while being enabling for the compound upadacitinib, does not reasonably provide enablement for

salt form of said compound. More specifically, the impugned application provides no specific worked examples of pharmaceutically acceptable salts as defined in claim 1. Claim 1 is therefore invalid for lack of enablement.

35. **Insufficiency of disclosure with regard to claims 1-2**: It has been amply asserted in the submissions made herein above that the specification of the impugned application lacks any data/information demonstrating that the claimed upadacitinib compound results in an enhanced therapeutic efficacy over the known JAK inhibitors, thereby rendering the application short of sufficient technical disclosure mandated by the Act.

PRAYER

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

i. that the Indian Patent Application No. **4759/DELNP/2012** made by ABBVIE INC, be rejected under Section 25(1) of the Patents Act;

ii. the Opponent may be allowed to file further documents as evidence if necessary, to support its averments;

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

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

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

Dated this 21 July 2023

Mr. Mohammad Yunus

IN/PA/2283

(Agent for the opponent)

To

The Controller of Patents

The Patent Office, Delhi