

# Gopakumar Nair Associates

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- Patents

- Trademarks

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- Contractual  
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- Technology  
Search,  
Sourcing and  
Transfer

- Licensing

- Prior Art  
Search

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- Patentability  
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- Revocation

- IP Enforcement  
and Legal  
Services

GNA/AF/029/17-18

10<sup>th</sup> July, 2017

To,  
The Controller of Patents  
The Patent Office (Head Office)  
Government of India, Boudhik Sampada Bhavan  
CP-2, Sector – V, Salt Lake City,  
Kolkata – 700 091

**Kind Attn: Dr. Jitendra Kumarpradhan,  
Deputy Controller of Patents & Designs**

Dear Sir,

**Sub: Pre-grant Representation/Opposition to the Patent Application  
under Section 25(1) of the Patents Act, 1970 and Rule 55(1) of  
the Patents Rules, 2003 (amended upto 2014)**

**Reg: Patent Application No. 3939/KOLNP/2010A published under  
Section 11A on 24<sup>th</sup> December, 2010.**

We are filing this Pre-grant representation/Opposition under Section 25(1) of the Patents Act, 1970 read with Rule 55(1) of the Patents Rule, 2003 on Form 7A. The Written Statement and evidence (attached herewith as Annexures/Exhibits) are enclosed herewith in duplicate.

As per provision of the Patent Act, 1970, we are entitled to file this Pre-grant Opposition any-time before grant of patent. As per the status available under inPASS, the Official website of the Indian Patent Office, the Application is under process.

Pune (Mrs. Srividya Ravi - Mobile: 09860010252)

*In Association with leading Patent and Trademark Attorneys globally.*

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This pre-grant opposition is being filed by us on behalf of Cancer Patients Aid Association. We request you to take this Pre-grant Opposition on record and process the same accordingly. In the meantime, we also draw your attention to our letter bearing reference no GNA/AF/028/17-18 dated 4<sup>th</sup> July, 2017 opposing the submission of alleged Expert Evidence by one Mr. William Shakespeare.

We further request you to provide to us a copy of the Reply Statement and evidence and further claim amendments, if any, filed by Patent Applicant. We also request you to grant us a personal hearing under Rule 55(1).

Also, please find enclosed herewith Form 26 (Power of Attorney), in original.

Thanking you in anticipation.

Kindly acknowledge receipt.

With best regards,

**Dr. Gopakumar G. Nair**  
**Regn. No: IN/PA 509**  
**Gopakumar Nair Associates**

Encl : as above

C.C: .D. P. Ahuja & Co. 14/2, Palm Avenue, Calcutta 700 019, INDIA.

Pune (Mrs. Srividya Ravi - Mobile: 09860010252)

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FORM 26  
THE PATENT ACT, 1970  
(39 of 1970)

FORM OF AUTHORISATION OF A PATENT AGENT / OR ANY PERSON  
IN A MATTER OR PROCEEDING UNDER THE ACT  
[See sections 127 and 132 and Rule 135]

We, Cancer Patients Aid Association (CPAA), a charitable non-governmental organization registered under Societies Registration Act, 1860 in January 1970 and under the Bombay Public Trusts Act, 1940 in February 1970, having registered office at 5, Malhotra House, Opposite GPO, Mumbai – 400 001, India hereby authorize Ms. Veena Johari, Advocate, Courtyard Attorneys, Ms. Julie George, Advocate, Dr. Gopakumar G. Nair, Dr. Aruna Sree, Ms. Andreyra Fernandes and Ms. Kavita Rao Parmar, of Gopakumar Nair Associates having office at 3<sup>rd</sup> Floor, 'Shivmangal', Akurli Road, Kandivli (East), Mumbai – 400 101, Maharashtra, India, to act on our behalf in relation to pursuing pre-grant and post-grant patent opposition and revocation related matters pertaining to

... 2





the National Phase Patent Application No. 3939/KOLNP/2010 filed at the Patent Office, Kolkata.

We request that all notices requisition and communication relating thereto may be sent to such person at the above address unless otherwise specified.

We hereby revoke all previous authorization, if any, made in respect of the same matter or proceedings.

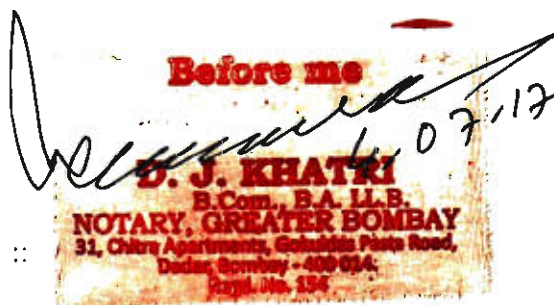
We hereby assent to the action already taken by the said person in the above matter.

Dated this 4th day of July 2017

*Shubha Maudgal*

Dr. Shubha Maudgal  
Executive Director  
Cancer Patients Aid Association (CPAA)

To  
The Controller of Patents  
The Patent Office  
At Kolkata



:: 2 ::



**BEFORE THE CONTROLLER OF PATENTS AT KOLKATA**

IN THE MATTER OF

Section 25(1) of The Patents Act, 1970, as  
amended up to The Patents (Amendment) Act,  
2005

And

IN THE MATTER OF

Rule 55 of The Patents Rules, 2003, as  
amended upto the Patents (Amendment) Rules,  
2016

And

IN THE MATTER OF

National Phase Patent Application No.  
**3939/KOLNP/2010** filed by Ariad  
Pharmaceuticals, Inc. on 21 October 2010  
claiming **priority from 21 May 2008**

..... APPLICANT

AND

IN THE MATTER OF:

Pre-grant representation by way of opposition  
Filed by the CANCER PATIENTS AID  
ASSOCIATION, a registered NGO, having its

registered head office at 5, Malhotra House,  
Opposite GPO, Mumbai – 400 001

..... OPPONENT

### **STATEMENT OF FACTS/ EVIDENCE**

1. It is respectfully submitted on behalf of Cancer Patients Aid Association (CPAA), a charitable organization registered under the Societies Registration Act, 1860 in January 1970 and under the Bombay Public Trusts Act, 1940 in February 1970, having its registered office at 5, Malhotra House, Opposite GPO, Mumbai – 400 001 (hereinafter referred to as “Opponent”) that a representation by way of opposition is being made against the grant of patent application titled: “PHOSPHOROUS DERIVATIVES OF KINASE INHIBITORS”, filed by the Applicant Ariad Pharmaceuticals, Inc., having its office at 26 Landsdowne Street, Cambridge, MA 02139, United States of America, bearing Indian Patent Application No. 3939/KOLNP/2010.

*It is submitted by the Opponent as follows:*

### **LOCUS STANDI**

2. That Representation by way of Opposition can be made by any person, in writing under Section 25(1) of the Patents Act, 1970. Notwithstanding, the Opponent submits that they are interested (under Sec. 2(1)(t)) in the field of the present invention and have *locus standi* to initiate the present pre-grant opposition proceedings. The Opponent has real and substantial interest in the aforesaid patent application being opposed.

### **JURISDICTION**

3. The patent application has been filed by Ariad Pharmaceuticals, Inc. at the Patent Office in Kolkata. Therefore, the Patent Controller has the jurisdiction to hear this pre-grant Opposition in Kolkata. The pre-grant opposition is being

filed on Form-7A under Section 25(1) of the Patents Act, 1970 as amended by the Patents (Amendment) Act, 2005 and Rule 55(1) of the Patents Rules, 2003 as amended by the Patents (Amendment) Rules, 2016. Any submission made or evidence adduced with specific reference to any subsection of Section 25(1) may be treated as being made without prejudice to other submissions made elsewhere in this Representation by way of Opposition.

4. The Applicant had initially filed the patent application with 22 claims. However, subsequently, the Applicant increased the claims to 72 claims. Nonetheless, after the filing the reply to the FER issued by the Learned Controller, it appears that the Applicant, at the time of hearing and on filing the written submissions, has made an application to reduce the 72 claims to only 2 claims, consisting of one structure – that of *brigatinib*. The Opponent submits that the claimed compound is not novel, lacks inventive step, and that the claimed compound is a mere derivative of a known compound and cannot be patented as it is hit by section 3 of the Patents Act. No patent ought to be granted to the Applicant on the present application.
5. The Opponent submits that the grant of the impugned patent application reciting amended Claims 1 and 2 is being opposed by availing strong and valid grounds provided under Section 25(1) of the Patent Act 1970 (amended up to date by the Patents (Amendment) Act, 2005) (hereinafter referred to as “the Act”) and is consequently filing the present representation/ pre-grant opposition to the present Application.

## **BACKGROUND**

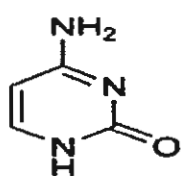
6. The present Application relates to a diaminopyrimidine structure, connected to a phenyl-piperidinyl-piperazinyl three ring moiety and is also connected to a phenyl ring substituted with a dimethylphosphoryl group. All of these structures are known and the claimed compound is not new, is obvious to a person skilled in the art and does not involve a technical advance.



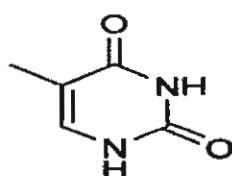
7. Pyrimidine structures have been known since 1818 and have been an important pharmacophore, interacting with nucleic acids, etc. used in medicines. Pyrimidine has been found to have excellent activity against tumour cells proved to be effective as an anti-cancer agent. Some diaminopyrimidines are used in anti-malarial drugs, have been used as effective anti bacteria or chemotherapeutic agents, containing pyrimidine moiety [See Lagoja, "Pyrimidine a constituent for natural biological active compounds" (2005) *Chemistry & Biodiversity* 1–50].
8. The compound claimed in the present application is for the treatment of patients with metastatic anaplastic lymphoma kinase (ALK) – positive non-small cell lung cancer(NSLC), who have progressed on or are intolerant to crizotinib.
9. Both tyrosine and ALK inhibitors have been known and used in cancer treatment. ALK inhibitors act on tumours with variations of ALK.
10. ALK, a member of the insulin receptor tyrosine kinase family (RTK) [Ullrich and Schlessinger, "Signal transduction by receptors with tyrosine kinase activity" (1990)*Cell* 61(2): 203–12], was first identified as part of the NPM-ALK oncogenic fusion protein, resulting from the translocation between chromosomes 2 and 5 associated with anaplastic large cell lymphoma [Morris, *et al.* "Fusion of a kinase gene, ALK, to a nucleolar protein gene, NPM, in non-Hodgkin's lymphoma" (1994) *Science* 263(5151): 1281–84]. The 2,5 chromosomal translocation is associated with approximately 60% anaplastic large-cell lymphomas (ALCLs). The translocation creates a fusion gene consisting of the ALK (anaplastic lymphoma kinase) gene and the nucleophosmin (NPM) gene: the 3' half of ALK, derived from chromosome 2 and coding for the catalytic domain, is fused to the 5' portion of NPM from chromosome 5. The product of the NPM-ALK fusion gene is oncogenic.



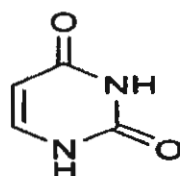
11. In 2007, Galkin, *et al.* described NVP-TAE684 as a selective inhibitor of NPM-ALK (nucleophosmin-anaplastic lymphoma kinase) [See Exhibit C hereto; Galkin, *et al.*, “Identification of NVP-TAE684, a potent, selective and efficacious inhibitor of NPM-ALK” (2007) *Proceedings of the National Academy of Sciences of the United States of America* 104(1): 270–75]. On 1 May 2008, McDermott, *et al.* described that genomic alterations of ALK may sensitise tumours to ALK inhibitors [See McDermott, *et al.*, “Genomic alterations of anaplastic lymphoma kinase may sensitise tumors to anaplastic lymphoma kinase inhibitors” (2008) *Cancer Research* 68(9): 3389–95].
12. It may be of importance to note that the deoxyribonucleic acid (DNA) is a molecule that carries genetic instructions used in the growth development of all known living organisms, including viruses. Most DNA molecules consist of two biopolymer strandscoiled to form a double helix. The two DNA strands are termed polynucleotides, and each nucleotide is composed of one of four nitrogen containing nucleobases – cytosine, guanine, adenine or thymine. The cytosine and thymine are classified as pyrimidines (with cytosine being an amino-substituted pyrimidine) – six membered rings, while the guanine and adenine are classified as purines – five and six membered heterocyclic compounds.



Cytosine (C)



Thymine (T)



Uracil (U)

The nucleobases – cytosine, guanine, adenine or thymine, are attached to a sugar called deoxyribose, and a **phosphate group**. The nucleotides are joined alternating between the sugar and phosphate backbone. The nitrogenous bases are bound together with base pairing rules with hydrogen bonds.

13. It is well known that phosphorous is the main element used for growth and repair of body cells. Phosphorous is essential to life and its derivatives are used in a multitude of technical / industrial applications.
14. Phosphorus compounds, in general, are the corner stone in pharmaceutical drugs. Many of these compounds exhibit antifungal, antibacterial, anticancer and significant analgesic/anti-inflammatory properties. Bisphosphonates and aminophosphonates, taken as representative examples, are important precursors of the corresponding bisphosphonic acid that is known to demonstrate, in many cases, remarkable pharmacologically interesting properties.
15. Piperidines are vital pieces of numerous widely-used drugs, are already pervasive in drug syntheses and serve as the centre of several widely used pharmaceuticals including morphine, *Plavix*, *Cialis*, and *Ritalin*. Piperidines have hexagonal structures with several sites open to the addition of functional groups, the reactive building blocks of organic molecules.
16. Various biologically active synthetic compounds have six-membered two-nitrogen containing heterocyclic ring in their structures, such as piperazine. Piperazines show numerous physiological effect such as anti-tuberculosis, anthelmintics, anti-anginals, anti-cancer, analgesic, antidepressant, anti-psychotic, anti-diabetic, antihistamines, hypolipidemic, and flavouring agent and these drugs have encouraged the medicinal chemists to synthesize a large number of novel chemotherapeutic agents.
17. What is claimed in the present Application is known, obvious to a person skilled in the art, lacks novelty and inventive step.

#### **PATENT APPLICANT'S MAIN CONTENTION**

18. The Patent Applicant, Ariad Pharmaceuticals, Inc., filed the present Application on 21 October 2010. The application is the national phase entry of

PCT Application PCT/US2009/044918 which was filed on 21 May 2009 claiming multiple priorities with the earliest priority date of **21 May 2008** and which was published on 24 December 2010 as WO 2009/143389. Bibliographic page along with the amended claims of present National Phase Application No. 3939/KOLNP/2010 retrieved from the Indian Patent Office website is enclosed herewith as **Annexure 1**.

19. The present Application now recites only two claims, though it had commenced with very broad markush claims. The compounds disclosed in the Specification are markush structures with many possible compounds. The recently amended claims are for a single structure of *brigatinib* and its salt form. There is now no claim to the pharmaceutical compositions or the process of making the compounds in the final amended claims.
20. The Applicant is claiming a compound that consists of a core pyrimidine structure, substituted with chloro at 5-position and unsubstituted 6-position, connected to phenyl-piperidinyl-piperazinyl three ring moiety at 2-position via a NH linker and connected to a phenyl at 4-position via NH linker, and this phenyl is substituted with a dimethylphosphoryl group.
21. The Applicant is seeking a patent on a known structure and a compound that is obvious to a person skilled in the art. The patent application should therefore be dismissed *in toto*.
22. The Opponent is filing this opposition as the claims of the Applicant are not a genuine therapeutic invention, lack novelty, lack inventive step and are obvious to a person skilled in the art. The compound as claimed in the application is a pyrimidine derivative with attachments of phosphorous derivatives. Pyrimidine structures and its derivatives are known to be effective kinase inhibitors prior to the priority of the present application. Phosphorous and its derivatives too have

been known for decades. The use of phosphorous derivatives as kinase inhibitor is obvious to a person skilled in the art.

23. The prior art annexed to the present Pre-Grant Opposition shows clearly that the claimed compound is known prior to the priority date of the present Application and does not involve an inventive step. The claims are not patentable under Section 3(d) of the Act. The grounds of opposition have been laid down herein below as being under section 25(1).
24. The Opponent states that in India lung cancer constitutes about 6.9 per cent of all new cancers and about 9.3 per cent of all cancer related deaths in both sexes [See Malik and Raina, “Lung Cancer: Prevalent trends and emerging concepts” (2015) *The Indian Journal of Medical* 141(1): 5–7]. Adenocarcinoma is a non-small cell lung carcinoma that has become one of the commonest sub-types found of lung cancer.
25. The Opponent further states that the right to health as guaranteed under Article 21 of the Constitution of India is paramount, and medicines required for the treatment of cancer, including non small cell lung carcinoma, ought to be made available at affordable prices to the people in the country. Wrongfully granting a patent to the Applicant would breach the right to life of many patients with cancer who ought to be able to obtain medicines at affordable prices. The price of *brigatinib* in the USA is very high (about USD 2500 for 30 tablets of 30mg – which would be approximately only 5 days dosage, if 180 mg per day needs to be consumed). This price is way beyond the reach of people in India. This is a monopolistic price, and if the patent is wrongly granted, it would prevent competition that could have otherwise helped to bring down the prices of the drugs, allowing people to get the drugs at an affordable price.

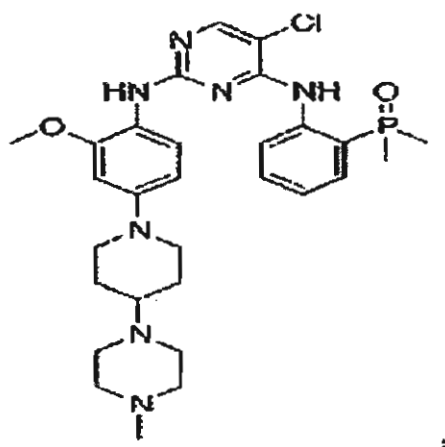
### **PRE-GRANT OPPOSITION ON THE FOLLOWING GROUNDS:-**

26. *Section 25(1): Opposition to the patent where the application has been published but not granted.* The following grounds and evidence sets out the basis of the opposition to the present Application. It is submitted that the impugned patent application claiming invention is not an invention within the meaning of Section 2(1)(j) of the Patents Act, is not new, does not involve an inventive step as defined under section 2(1)(ja) and is not a new invention as defined under section 2(1)(l) as it has been anticipated by prior publication. Under section 3(d) of the Act, derivatives, salts, esters, etc. of known substances are not patentable. Pyrimidine, diaminopyrimidine, piperidinyl, piperazinyl, phenyl, dimethylphosphoryl groups are known in science, whose properties and significance are also known prior to the priority date of the Applicant.
27. In any event, no patent ought to be granted on the present Application, and the Opponent is opposing both the claims for phosphorous derivatives as kinase inhibitors, that describe *brigatinib*, on several grounds. For reasons set out in detail below, the claims of the present Application for phosphorous derivatives as kinase inhibitors are not patentable under the Act, and the present Application should be rejected.
28. The Opponent is filing this pre-grant opposition on the grounds stated in Section 25(1) of the Patents Act. The primary grounds of opposition are under (i) Section 25(1)(b)—that the invention so far claimed has been published before the priority date of the claim; (ii) Section 25(1)(d)—as the methods of making the derivatives are all known and their properties are known, (iii) Section 25(1)(e)—as the invention so claimed is obvious and clearly does not involve an inventive step and (iv) Section 25(1)(f)—as the invention so claimed is not patentable in India under the Act. Section 25(1)(g) is also attracted as the Complete Specification accompanying the present Application do not sufficiently and clearly describe the alleged invention.

29. The primary grounds of opposition under section 25(1) that the invention so far claimed has been published and claimed before the priority date of the claims in the following list of documents filed herewith:
- (a) **Exhibit A:** WO 03/078404 A1 titled “Pyrimidine derivatives” filed by Novartis AG and published on 25 September 2003.
  - (b) **Exhibit B:** WO 2004/080980 A1 titled ““2-4 Di (phenylanimino) pyrimidines useful in the treatment of neoplastic diseases, inflammatory and immune system disorders” filed by Novartis AG and published on 23 September 2004.
  - (c) **Exhibit C:** Galkin, *et al.*, “Identification of NVP-TAE684, a potent, selective and efficacious inhibitor of NPM-ALK” (2007) *Proceedings of the National Academy of Sciences of the United States of America* 104(1): 270–75.
  - (d) **Exhibit D:** Zhao, *et al.* “The synthesis of novel acetolactate synthase inhibitors, N-(asymmetrically disubstituted phosphoryl)-N’-(4,6-dimethoxypyrimidin-2-yl) Ureas”, (1999) *Heteroatom Chemistry* 10(3): 237–41.
  - (e) **Exhibit E:** Abstract: Zhao, *et al.*, “Bioisostere of sulfonyl moiety – The synthesis of new ALS inhibitors N-(asymmetry disubstituted phosphoryl)-N’-(4,6-dimethoxypyrimidin-2-yl) Ureas”, (1998) *Chinese Chemical Letters* 5: 455–58.
  - (f) **Exhibit F:** Abstract: Zhao, *et al.*, “Bioisoterism between sulfonyl group and phosphoryl group – The synthesis of new ALS inhibitors N-(arylamino hydroxyl phosphoryl)-N’-(4,6-dimethoxypyrimidine-2-yl) ureas”, (1998) *Chinese Chemical Letters* 8: 723–24 + 275
  - (g) **Exhibit G:** Schneider and Benner, “Building blocks for oligonucleotide analogs with dimethylene-sulfide, -sulfoxide, and -sulfone groups replacing phosphodiester linkages” (1990) *Tetrahedron Letters* 31(3): 335–38.
30. The Opponent states that none of the claims of the Applicant should be deemed accepted, unless specifically admitted/ accepted herein. The Opponent is

opposing all the claims of the Application and states that the patent application should be dismissed *in toto*.

31. The grounds of opposition of claims 1 and 2 are primarily based on provisions of Section 25(1) read with Sections 2, 3, 10 and of the Act as specified hereto.
32. The Opponent states that the Applicant has made claims for the following structures, which have been known for many decades prior to the priority date of the present Application, and are also obvious to a person skilled in the art. Thus, no claim for a patent can be made by the Applicant.
33. The claims of the Applicant relates to the same structure at Claim 1 and at Claim 2, that is, the structure of *brigatinib*; with Claim 1 also including a pharmaceutically acceptable salt thereof:



34. As it can be seen the structural components of the Applicant's claim consist of
- (a) Pyrimidine core structure
  - (b) Pyrimidine substituted with a chloro at 5-position and unsubstituted at 6<sup>th</sup> position
  - (c) Pyrimidine connected to a phenyl-piperidinyl-piperazinyl three-ring moiety at 2-position via a NH linker
  - (d) Pyrimidine connected to a phenyl at 4-position via a NH linker, and this phenyl is substituted with a dimethylphosphoryl group.



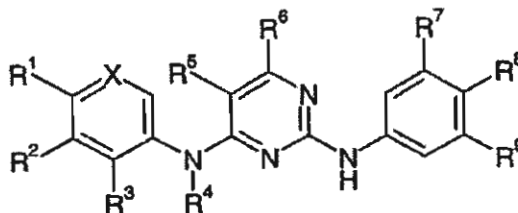
35. The prior art documents annexed to this opposition specifically show such substitutions and disclose the similarities between the claimed structures in the present application and the prior art documents annexed to this Pre-grant Opposition.

### GROUND OF OPPOSITION

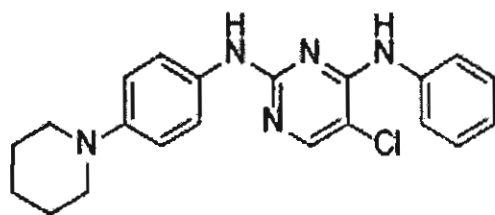
36. The Opponent now deals with following relevant grounds of pre-grant opposition under Section 25(1) substantiated with facts disclosed in the prior art documents.

**a. Section 25(1)(b):Lack of Novelty/ Prior publication**

- (i) The Opponent submits that the impugned patent application is ineligible for grant of patent under Section 25(1)(b) of the Patents Act, 1970.
- (ii) The core structure or basic scaffold of the compound claimed in the impugned patent application is a pyrimidine structure as described above.
- (iii) The core compound of the alleged invention in the impugned Application is clearly described and anticipated in the document at **Exhibit A (WO 03/078404 A1)**, bearing priority date of 15 March 2002 and titled “Pyrimidine derivatives” that claims the following core structure:

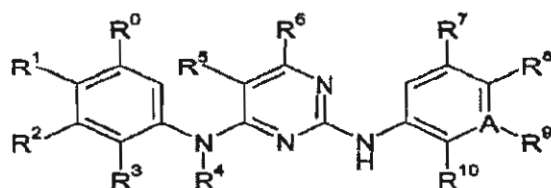


- (iv) In the above structure when R<sup>5</sup> is halogen (which includes –Cl), R<sup>6</sup> is –H, R<sup>8</sup> includes C<sub>3</sub>-C<sub>8</sub>cycloalkyl, and X is CR<sup>0</sup> with R<sup>0</sup> being –H, the following compound is disclosed. {See pages 8 to 20 of **Exhibit A**}.

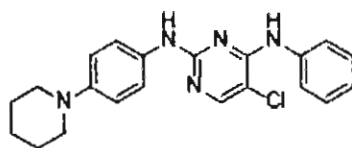


- (v) The genus of the structure as claimed in the present Application, as shown here above, is anticipated and described at Exhibit A to this pre-grant opposition.
- (vi) **Exhibit A** hereto also claims pharmaceutical acceptable salts, for use as a pharmaceutical, thereby destroying the novelty of Claim 1 of the present Application.
- (vii) With regard to biological activity, **Exhibit A** hereto discloses compounds of the core pyrimidine derivatives that are administered either as the sole active ingredient or together with other drugs, is useful against neoplastic diseases, inflammatory disorders, or in immunomodulating regimens. The specification describes the combination drugs to include drugs anti-neoplastic anti-metabolites, including phosphates, anti-proliferating agents like bisphosphates, alkylating agents like cyclophosphamide.
- (viii) The compound disclosed in **Exhibit A**, that is, pyrimidine derivatives, is used as inhibitors for the treatment of or prevention of a disease or condition in which ZAP-70, FAK and/ or Syk tyrosine kinase activation plays a role. The compound is used as an anti-cancer agent and prevention and treatment of tumours amongst other diseases such as autoimmune diseases, diabetes, etc.
- (ix) In fact, Exhibit A reveals the compound and its derivatives that **decrease the protein kinase activity** and further anti-angiogenic compounds used - **includes, but is not limited to** compounds which decrease activity, eg. Vascular Endothelial Growth Factor, Bcr – Abl tyrosine kinase, Flt-3 and insulin like growth factor I receptor, cyclin dependent kinase, etc.

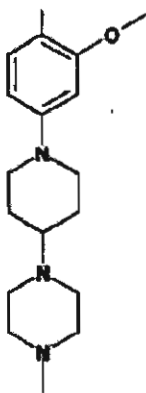
- (x) It also reveals compounds inhibiting c-Src protein tyrosine kinase activity include, but not limited to, compounds belonging to the structure classes of pyrazopyrimidines, etc.
- (xi) Exhibit A reveals that it is these core compounds of **pyrimidine derivatives that are used as inhibitors of protein tyrosine kinase**. The Applicant attempts to show the exact same inhibition that has been revealed years ago, by specifying ALK inhibition. But, the compounds disclosed at Exhibit A are inclusive and not exhaustive, and Exhibit A discloses the properties of pyrimidine derivatives as tyrosine protein inhibitors. Thus, there is no novelty in the claim of the Applicant herein.
- (xii) Exhibit A also reveals that the concentration of test compounds resulted in 50% inhibition ( $IC_{50}$ ) determined from dose response curves. In the assay, the compounds of the invention had  $IC_{50}$  values in the range of 100 nM to 10  $\mu$ M, preferably from 100 to 1  $\mu$ M. Compound of example 128 at Exhibit A had  $IC_{50}$  value of 150 nM. {See page 23 read with page 15 of Exhibit A}.
- (xiii) The genus of the structure claimed in the present Application is also anticipated in the document annexed hereto as **Exhibit B (WO 2004/080980)**, bearing priority date of 14 March 2003 and titled “2-4 Di (phenylanimo) pyrimidines useful in the treatment of neoplastic diseases, inflammatory and immune system disorders”. The claimed structure at Exhibit B is



When  $R^5$  is halogen (which includes  $-Cl$ ),  $R^6$  is hydrogen,  $R^4$  is hydrogen, A is C, and  $R^8$  is 6 membered heterocyclic ring comprising of 1 N apart from other substitutions, the following core structure of the claimed compound overlaps with the core structure of *brigatinib*.



- (xiv) **Exhibit B** also reveals pyrimidine connected to a phenyl-piperidinyl-piperazinyl three-ring moiety at 2-position via a NH linker {See page 67 example 19-4; page 77 example 20-18, page 96 example 27-9, page 98 example 28-5, page 106 example 30-7, and has been claimed at page 175–176}.



- (xv) **Exhibit B** also reveals the preparation of methoxy phenyl-piperidinyl-piperazinyl three-ring moiety {See page 132 of Exhibit B and more particularly the method at page 139 example 46-5, identified at page 144 examples 46–29}.
- (xvi) Exhibit B also claims the pharmaceutically acceptable salts and compositions of the compound.
- (xvii) The document at **Exhibit B**, apart from revealing the use of the compounds as inhibitors of ZAP-7 protein tyrosine kinase, IGF-IR (insulin like growth factor receptor 1) inhibitor, also reveals the compound as an FAK inhibitor to be used as a drug for anti-tumour growth and metastasis. The compounds of the invention at **Exhibit B** are disclosed for use for treating neoplastic disease, in particular breast tumour, cancer of the bowel (colon and rectum), stomach cancer, cancer of the ovary, prostate, **non-small cell lung cancer**, small cell lung cancer, cancer of liver, melanoma, bladder tumour, cancer of head and neck, etc. The compound disclosed at **Exhibit B** also exhibits powerful

inhibition of **tyrosine kinase activity of anaplastic lymphoma kinase (ALK)** and the fusion protein of **NPM-ALK** {See pages 16 to 18 and 24 of Exhibit B}.

- (xviii) The Applicant in the present Application describes the alleged invention for use as ALK tyrosine kinase inhibitor. However, the structure as revealed in **Exhibit B** anticipates and is almost identical to the structure claimed by the Applicant herein. The substitution of the sulphonyl group as revealed in Exhibit B is replaced by the phosphoryl group in the present Application. Such substitution does not make the alleged invention novel, nor does it involve an inventive step, as is explained hereinbelow.
- (xix) Such similar pyrimidine structures have also been revealed in other published documents. For instance, WO 2005/016894 A1 discloses pyrimidine derivatives for the treatment or prevention of disease that respond to the inhibition of FAK and/ or ALK and / or ZAP-70 and /or IGF-IR.
- (xx) Another patent document, WO 2006/133426, also reveals compounds similar to the core structure in the present Application. The compound is claimed to be used for the treatment of conditions in which modulation of the JAK pathway or inhibition of JAK kinases, particularly JAK3 may be therapeutically useful.
- (xxi) The above documents show the use of pyrimidine core structures as tyrosine kinase inhibitors. This demolishes the novelty of the claims of the present Application, as all that the Applicant is showing through the present Application is, at most, a new use of a known compound.

**b. Section 25(1)(d) : Prior public knowledge or public use in India**

- (i) It is stated that the invention so far claimed in Claims 1 and 2 of the impugned patent application was publicly known before the priority date of these claims. As can be seen from the prior art documents (**Exhibits A to G**) cited in the present Pre-grant Opposition, there exists prior

public knowledge of alleged invention claimed in the impugned patent application prior to the priority date of said patent application.

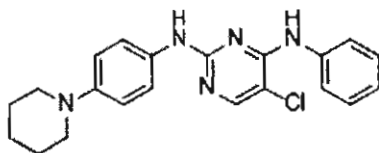
- (ii) Claims 1 and 2 of the impugned patent application, of pyrimidine derivatives used as ALK inhibitors has been known prior to the priority date of the Applicant. Therefore, the impugned application ought to be rejected on the ground of prior public knowledge under Section 25(1)(d) of the Act.

**c. Section 25(1)(e) : Obviousness and Lack of inventive step**

- (i) The Opponent submits that the alleged invention clearly lacks an inventive step and is obvious to a person of ordinary skill in the art. As such the Indian Patent Application 3939/KOLNP/2010 is ineligible for grant of patent under section 25(1)(e) of the Act.
- (ii) The substitution of sulphonyl groups with phosphoryl groups is obvious to a person skilled in the art as phosphoryl groups are known to be a good bioisostere, as explained in the documents at **Exhibit D to G** herein below.
- (iii) The activity of the claimed compound as a kinase inhibitor in the impugned Application is known and obvious to a person with skill in the art. Pyrimidine derivatives have known properties and were already found to be useful as inhibitors of ALK tyrosine kinase and would be the natural and obvious choice of a person skilled in the art to use it as an ALK tyrosine kinase inhibitor.
- (iv) Further, use of a phosphorous derivative (phosphoryl group) is also obvious to a person skilled in the art. The impugned application claims a previously known pyrimidine derivative with a sulphonyl group (called TAE684 and as has been disclosed in Exhibit B hereto) substituted with a phosphoryl group now identified as *brigatinib*). Such substitution does not reduce or enhance the properties and use of the core structure of pyrimidine derivatives to act as a tyrosine kinase inhibitor. Such

substitution has been known in the art and is obvious to a person skilled in the art.

- (v) Section 25(1)(e) provides a ground of opposition on the ground that the invention so far is claimed in a claim of complete specification is obvious and clearly does not involve any inventive step, having regard to the matter published, *inter alia*, in India or elsewhere in any other document.
- (vi) Section 2(1)(ja) defines inventive step thus: “‘inventive step’ means a feature of an invention that involves technical advance as compared to existing knowledge or having economic significance or both and that makes the invention not obvious to a person skilled in the art” (emphasis supplied).
- (vii) Thus, to possess inventive step, the invention must have a feature that (i) involves technical advance as compared to existing knowledge and (ii) is not obvious to a person skilled in the art. It is an established position of law that both these elements set out in the definition of “inventive step” have to be satisfied.
- (viii) As shown below, the Claims of the present Application are obvious to a person skilled in the art. Further, they do not involve any technical advance compared to existing knowledge. Therefore, they lack inventive step.
- (ix) As shown in the discussion above, Exhibit A and Exhibit B above disclosed that compounds with the following pharmacophore possess anti-cancer activity.



- (x) Further, Exhibit WO '980 (Exhibit B) disclosed a compound with the following structure, which is identified in subsequent literature as TAE-684 or NVP-TAE 684.



- (xi) *Ex facie*, a structural comparison shows that the compounds are structurally very similar, with the only difference being that the sulfonyl group in TAE-684 is replaced with a phosphoryl group in *brigatinib*.
- (xii) As will be shown below, this substitution does not involve an inventive step as (i) it is obvious to a person skilled in the art and (ii) it does not constitute a technical advance compared to existing knowledge.

**A. Substitution of sulfonyl group with phosphoryl group was obvious to a person skilled in the art**

- (xiii) Galkin, *et al.*, in “Identification of NVP-TAE684, a potent, selective and efficacious inhibitor of NPM-ALK”, (2007) *Proceedings of the National Academy of Sciences of the United States of America* 104(1): 270–275, a copy of which is hereto annexed and marked as “**Exhibit C**” described the ALK-inhibiting activity of TAE-684, a compound with a central core of diamino-pyrimidine attached to phenyl substitutions and containing a sulfonyl group.
- (xiv) Galkin, *et al.* (**Exhibit C**) disclosed that TAE-684 inhibited growth of NPM-ALK-transformed cells with an  $IC_{50}$  of  $\approx 3$  nM.
- (xv) Thus, in addition to Exhibits A and B, Galkin, *et al.* (**Exhibit C**) further established a compound with a central core of diamino-pyrimidine attached to phenyl substitutions as having potent ALK activity.
- (xvi) The sulfonyl group, which is present in TAE-684, was known to act as a privileged group for activity on various receptor targets.
- (xvii) Sulfonyl group-containing compounds, which mainly include sulfones and sulfonamides, have been studied for decades because of their significant roles in developing therapeutics for a number of diseases. Sulfonyl group-containing compounds constitute an important class of therapeutic agents in medicinal chemistry presumably because of the tense chemical structure and functionality of the sulfonyl, which could not only form hydrogen bonding interactions with active site residues of biological targets but also, as incorporated into core ring structure,

constrain the side chains and allowed their specific conformations that fit the active sites.

- (xviii) Sulfonyl compounds have been identified for use as anti-infectives, anti-cancer agents [Jain, *et al.*, "Sulfonyl-containing aldophosphoamide analogues as novel anticancer prodrugs targeted against cyclophosphamide-resistant tumor lines" (2004) *Journal of Medicinal Chemistry* 47:3843–52], carbonic anhydrase inhibitors [Wilkinson, *et al.*, "Inhibition of carbonic anhydrases with glycosyltriazole benzene sulphonamides" (2008) *Journal of Medicinal Chemistry* 51: 1945–53], CNS-acting agents [Sikazwe, *et al.*, "Binding of sulfonyl-containing arylalkylamines at Human 5-HT<sub>6</sub> serotonin receptors" (2006) *Journal of Medicinal Chemistry* 49: 5217–25] and anti-diabetic agents[US 2006/0276494 A1]. The Opponent craves leave to refer to and rely upon these references as and when required.
- (xix) Therefore off-target effects would be expected for compounds having sulfonyl group, especially off-target effect on targets playing role in diabetes such as insulin receptor.
- (xx) Galkin, *et al.* (**Exhibit C**) noted the homology between ALK and InsR and nonetheless reported greater selectivity of TAE-684 for ALK over InsR. Therefore, the anti-cancer activity having been attributed to the central core of diamino-pyrimidine attached to phenyl substitutions, a logical approach for modification of TAE-684 would be substitution of the sulfonyl group.
- (xxi) In light of the findings reported for TAE-684, a person skilled in the art who wanted to design a further selective inhibitor of ALK would consider replacing the sulfonyl group which could have off-target effects with a suitable bioisostere. This would thereby impart selectivity towards the desired target of interest.
- (xxii) For developing selective analogues of TAE-684 such that the compounds so designed would be devoid of or would have lesser affinity towards the insulin receptor, it would be appropriate to modify

the sulfonyl group by replacing it with a suitable bio-isostere. One such isosteric replacement known in the art was the replacement of the sulfonyl group with a phosphoryl group. This strategy was successfully implemented and reported, in the 1990s, for the design of acetolactate synthase inhibitors by Zhao, *et al.* in “The synthesis of novel acetolactate synthase inhibitors, N-(asymmetrically disubstituted phosphoryl)-N’-(4,6-dimethoxypyrimidin-2-yl) Ureas”, (1999) *Heteroatom Chemistry* 10(3): 237–41, a copy of which is hereto annexed and marked as “**Exhibit D**”. The close homology between the sulfonyl and phosphoryl groups in terms of size, bond angle, bond length, and configuration and previously published literature led the researchers to further explore the good degree of isosterism exhibited by sulfonyl and phosphoryl group. The bioisosterism between the sulfonyl group and the phosphoryl group was also reported by the same researchers in other publications in which they reported that the phosphoryl group was a good bio-isosteric replacement for the sulfonyl group [see (i) Zhao, *et al.*, “Bioisostere of sulfonyl moiety – The synthesis of new ALS inhibitors N-(asymmetrically disubstituted phosphoryl)-N’-(4,6-dimethoxypyrimidin-2-yl) Ureas”, (1998) *Chinese Chemical Letters* 5: 455–58 (abstract) and (ii) Zhao, *et al.*, “Bioisosterism between sulfonyl group and phosphoryl group – The synthesis of new ALS inhibitors N-(arylamino hydroxyl phosphoryl)-N’-(4,6-dimethoxypyrimidine-2-yl) ureas”, (1998) *Chinese Chemical Letters* 8: 723–24 + 275 (abstract), copies of which are hereto annexed and marked as “**Exhibit E**” and “**Exhibit F**” respectively.] Presently, only the abstracts of Exhibits E and F are available. The Opponent craves leave to refer to and rely upon the full text of these articles as and when available.

- (xxiii) Previously, Schneider and Benner in “Building blocks for oligonucleotide analogs with dimethylene-sulfide, -sulfoxide, and -sulfone groups replacing phosphodiester linkages” (1990) *Tetrahedron Letters* 31(3): 335–38, a copy of which is hereto annexed and marked as

**“Exhibit G”** had successfully implemented and reported a reverse strategy of replacing phosphodiester linkage with sulfonyl group to overcome the drawbacks associated with the phosphodiester bond.

- (xxiv) Thus, as reported in **Exhibits D to G**, the promising bioisosterism between the sulfonyl and phosphoryl groups had already been established in the prior art.
- (xxv) Thus, a person skilled in the art would consider replacing the sulfonyl group of TAE-684 with its bioisostere, a phosphoryl group, to reduce the likelihood of off-target effects on account of the presence of the sulfonyl group, thereby arriving at the claimed compound, *brigatinib*.
- (xxvi) Summarily, the ALK-inhibiting activity of the central core of diamino-pyrimidine attached to phenyl substitutions was known in the art. Therefore, a logical approach for modification of TAE-684 for greater selectivity for ALK would be substitution of the sulfonyl group. Bioisosteric substitution of the sulfonyl group with the phosphoryl group had already been reported. Thus the substitution of the sulfonyl group in TAE-684 with a phosphoryl group providing the claimed compound, *brigatinib*, was obvious to a person skilled in the art.
- (xxvii) Therefore, Claims 1 and 2 of the present Application are obvious to a person skilled in the art.

**B. Substitution of sulfonyl group with phosphoryl group does not involve a technical advance as compared to existing knowledge**

- (xxviii) The alleged invention also does not involve any technical advance compared to existing knowledge.
- (xxix) In the Complete Specification, the Applicant sets out that the invention is directed to new classes of compounds useful as protein-kinase inhibitors that would be useful in treating protein-kinase related diseases caused by abnormal protein kinase activity [Complete Specification, page 1, lines 5–18].

- (xxx) However, save for a few sweeping generalised statements regarding the activity of the claimed classes of compounds, the Complete Specification does not disclose the potency of the claimed compound, *brigatinib*, for any kinase activity. It therefore does not disclose a technical advance in terms of ALK inhibitory activity or potency for the claimed compound.
- (xxxi) In its written submissions and affidavit filed on or about 28 June 2017, the Applicant is belatedly attempting to show an unexpected therapeutic advantageous effect by showing that the InsR inhibition, now described as an undesired side-activity, is allegedly weaker than the InsR inhibition exhibited by TAE-684.
- (xxxii) This is not permissible for several reasons which are in addition to and without prejudice to one another. Summarily, (i) the Complete Specification is silent on the alleged technical advance compared to existing knowledge and does not make it plausible; (ii) The accompanying affidavit does not meet the requirements of the Indian law; (iii) The Applicant is basing the case of alleged technical advance on post-filing data; and (iv) the data to establish the alleged technical advance is incomplete.

B.1. The Complete Specification is silent on the alleged technical advance and does not make it plausible

- (xxxiii) The Complete Specification accompanying the present Application does not mention the side-effect of InsR inhibition as a problem to be solved or weaker or less potent InsR inhibition as an unexpected effect found for the compounds of the alleged invention.
- (xxxiv) Indeed, more particularly, the alleged invention as per the Complete Specification is to provide ALK tyrosine kinase inhibitors of ALK, fak and cmet [Complete Specification, page 103, lines 10–20].
- (xxxv) In fact, one of the characteristics set out by the Applicant for the alleged invention is that it would *inter alia* have “a cytotoxic or growth

inhibitory effect on cancer cell lines maintained in vitro or in animal studies” and that especially preferred are “compounds of the invention which inhibit proliferation of Ba/F3 NMP-ALK, Ba/F3 EML4-ALK, Karpas 299 and/or SU-DHL-I cells with a potency at least as great as the potency of known ALK inhibitors such as NVP-T AE684 and PF2341066 among others, preferably with a potency at least twice that of known ALK inhibitors, and more preferably with a potency at least 10 times that of known ALK inhibitors as determined by comparative studies.” [Complete Specification, pages 52–53] (emphasis supplied)

- (xxxvi) Therefore, the technical advance as canvassed by the Applicant in its Complete Specification is the provision of ALK inhibitors with potency as great as or twice or at least 10 time that of known ALK inhibitors.
- (xxxvii) The Complete Specification accompanying the present Application is completely silent on the adverse or off-target effects of other known ALK kinase inhibitors and does not identify it as a problem that needed to be solved. On the contrary, the desired characteristic of the compounds of the alleged invention is that it must be as potent or more potent than known ALK inhibitors, including TAE 684.
- (xxxviii) It is an established position of law that the alleged advance or advantage or effect, if any, to support an inventive step must be made plausible by the Complete Specification. The Complete Specification is completely silent on this alleged advantage or effect of weaker InsR inhibitory activity.
- (xxxix) Therefore, data to show an alleged weaker or less potent InsR inhibition exhibited by the claimed compound(s) cannot be introduced as an argument or evidence and, even if introduced, is not relevant to the determination of the inventive step or lack thereof for the present Application.
- (xl) It appears that the Application is attempting to divert the attention of the Learned Controller by attempting to show an alleged advance by

providing comparative data for InsR activity, an off-target activity, rather than ALK- inhibitory activity.

*B.2. The accompanying affidavit does not meet the requirements of the Indian law*

- (xli) Without prejudice to the above and in addition thereto, the Applicant has furnished an affidavit of one Dr. William C. Shakespeare, one of the co-inventors, to introduce data regarding the alleged weaker InsR inhibitory effect displayed by the claimed compound over a known prior art compound, TAE-684.
- (xlii) The said affidavit does not meet the requirements of the Indian law and lacks evidentiary value.
- (xliii) Rule 126 of the Patents Rules, 2003 stipulates that an affidavit sworn in any country or place outside India is to be sworn before a diplomatic or consular officer, within the meaning of the Diplomatic and Consular Officers (Oaths and Fees) Act, 1948 in such country or place or before a notary of the country or place recognized by the Central Government under section 14 of the Notaries Act, 1952 or before the Judge or Magistrate of the country or place. Under Section 14 of the Notaries Act, 1952, reciprocal arrangements of recognition of notarial acts done by foreign notaries need to be recognized by the Central Government. It appears that the said affidavit was sworn before a notary public in the United States of America. The Central Government has not notified the United States of America under section 14 of the Notaries Act, 1952. Therefore, the said affidavit does not meet the requirements of the Indian law.
- (xliv) Further, the said affidavit has only been notarised and has not been apostilled. The Ministry of External Affairs has, on its website, clearly states that only documents apostilled in Member countries of the Hague Convention Abolishing the Requirement of Legalisation for Foreign Public Documents, 1961 are acceptable. Both India and the United



States of America are members of the Hague Convention, in which documents need to be Apostilled to be considered as authentic.

- (xlv) Thus, neither has the said affidavit been duly notarised as required under the Indian patent law nor has it been apostilled.
- (xlvi) Additionally, the deponent of the affidavit declares that “all the statements made in paragraphs 1 to 3 of the foregoing affidavit are true to my knowledge **and** that all statements made on information and belief are believed to be true.” (emphasis supplied) The declaration is self-contradictory in as much as it first states that all statements made in paragraphs 1 to 3 are true to the knowledge of the deponent and then states that all statements made on information and belief are believed to be true. Indian law requires the deponent to specifically identify statements which are based on personal knowledge and those based on information received and believed to be true. The deponent does not identify the statements of the affidavit which are made based on information which is believed to be true nor does he identify the source of the information.
- (xlvii) The said affidavit therefore does not meet the requirements of the Indian law and cannot be admitted a legal document with evidentiary value to be considered in the proceedings.

*B.3. The Applicant is basing the case of alleged technical advance on post-filing data*

- (xlviii) Without prejudice to the above and in addition thereto, the said affidavit does not provide details as to when the tests were conducted.
- (xlix) Given that this data is not mentioned in the Complete Specification accompanying the present Application, it ought to be presumed that the evidence has been generated after the priority date and the filing date and merely for the purposes of submission to patent offices to show an alleged technical advance for the claimed compound(s).

- (i) Further, as stated above, the deponent does not identify which part of his statement is based on information he believes to be true. This is particularly relevant as the deponent states that he was “previously employed by” Ariad Pharmaceuticals, Inc., the inventor. It is therefore unclear as to whether the information submitted by the deponent regarding the alleged InsR inhibition activity was generated by the deponent or during his employment with Ariad Pharmaceuticals, Inc. and the basis on which he makes the statements providing the data regarding the alleged InsR inhibition activity.
- (li) It must be presumed that the data regarding the alleged technical advance, i.e. InsR inhibition, submitted vide the affidavit of Dr. Shakespeare is post-filing data.
- (lii) It is an established position of law in India that post-filing alleged evidence is not permissible to show an inventive step.
- (liii) Therefore, the data showing the alleged technical advance cannot be considered to be relevant to the determination of the technical advance of the present Application.

B.4. The data to establish the alleged technical advance is incomplete

- (liv) Without prejudice to the above and in addition thereto, even the comparative data to establish the alleged technical advance of weaker InsR inhibition is incomplete.
- (lv) It appears from the affidavit of the said Dr. Shakespeare that the data reports the results of an enzymatic InsR inhibition assay to assess the enzyme inhibition exhibited by the claimed compound, *brigatinib*, and NVP-TAE684. The results so obtained indicate that *brigatinib* has an IC<sub>50</sub> of 196 nM while NVP-TAE684 exhibits a value of 2 nM indicating many-fold less activity of *brigatinib* towards InsR enzyme. On the basis of this data, the Applicant is alleging a technical advance.
- (lvi) The Applicant itself refers Galkin, *et al.* (**Exhibit C**) as the reference point for this comparison provided by it.

- (lvii) However, Galkin, *et al.*(**Exhibit C**) particularly noted the discrepancy between the cellular and *in vitro* biochemical assay for InsR. Galkin, *et al.* also noted that a similar discrepancy in cellular and biochemical assays was reported by Garcia-Echeverria, *et al.* in (2004) Cancer Cell 5:231–239 [Galkin, *et al.*, page 271, LHC].
- (lviii) Galkin, *et al.*(**Exhibit C**) reported that“when TAE684 was tested against recombinant InsR in an in vitro kinase assay an IC of  $\approx 10\text{--}20$  nM was obtained in various independent experiments”[Galkin, *et al.*, page 271, LHC, para 1, line 4]. Further with respect to cellular assay results, they reported “[i]n marked contrast to the enzymatic data, a concentration of  $> 1$   $\mu\text{M}$  TAE684 was required to block insulin-induced phosphorylation of InsR, Akt, and FKHR, which is  $\approx 100$ -fold higher than the concentration required to inhibit cellular NPM-ALK activity”[Galkin, *et al.*, page 271, LHC, para 1, line 14).
- (lix) The cellular assay systems would better mimic the physiological conditions as opposed to *in vitro* enzymatic assay results. Therefore, in order to obtain a correct understanding of InsR inhibition, especially for the purpose of comparison, it would be ideal to compare both the enzymatic assay results as well as the cellular assay results.
- (lx) However, the Applicant has based the comparison on only enzymatic assay results which will, as reported by Galkin, *et al.*, not give a thorough understanding of the activity. The data is therefore incomplete.

#### B.5. Summary re alleged technical advance

- (lxi) As shown above, (i) the Complete Specification is silent on the alleged technical advance compared to existing knowledge and does not make it plausible; (ii) The accompanying affidavit does not meet the requirements of the Indian law; (iii) The Applicant is basing the case of alleged technical advance on post-filing data; and (iv) The data to establish the alleged technical advance is incomplete. Therefore, the affidavit of Dr. William C. Shakespeare ought not to be taken on record

and the contents thereof ought not to be considered as relevant evidence for the purpose of showing an alleged technical advance compared to existing knowledge or non-obviousness for the claimed compound over the known prior art.

**C. Conclusion**

- (lxii) As shown above, the ALK-inhibiting activity of compounds with a central core of diamino-pyrimidine attached to phenyl substitutions, including TAE-684, was known in the art. Because of the known bio-isosterism, the substitution of sulfonyl group with phosphoryl group was obvious to a person skilled in the art.
- (lxiii) It is therefore submitted that a person skilled in the art on combining the disclosures contained in prior art documents set out at Exhibits A, B and / or C with the disclosures contained in prior art documents set out at Exhibits D to G, would have a reasonable expectation of success and arrive at the alleged invention claimed in the present Application.
- (lxiv) Further, as shown above, the Applicant has not, in its Complete Specification, pleaded or shown any technical advance compared to existing knowledge for the claimed compounds.
- (lxv) Further, pharmaceutically acceptable salts and compounds of the claimed structure in the present impugned application are also obvious to a person with skill in the art.
- (lxvi) Therefore, Claims 1 and 2 are clearly obvious to a person skilled in the art and further do not involve any technical advance and ought to be rejected *in toto* under section 25(1)(e) read with section 2(1)(ja) of the Act.

**d. Section 25(1)(f): Not an invention within the meaning of the Patents Act.**

- (i) It has been shown by the prior art documents annexed in the present Pre-grant Opposition that the complete specification and the amended claims

do not constitute an invention. The alleged invention so far claimed is neither a new product nor a new process nor does it involve an inventive step as there is no technical advance as compared to existing knowledge and the alleged invention is obvious to a person skilled in the art.

- (ii) Thus the claims of the present Application does not meet the test prescribed under Sections 2(1)(j) and 2(1)(ja) of the Act and hence the application ought to be dismissed *in limine*.

**Section 3(d): Lack of therapeutic efficacy– Sec. 3(d) of the Act**

- (i) The Opponent strongly submits that the alleged invention falls within the ambit of Section 3(d) and hence is not patentable. The definition of Section 3(d) read alongwith explanation is relevant and validly applicable for the alleged subject matter.
- (ii) Sec. 3(d) of the Act reads as “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”**is not patentable under the Act.**

*Explanation:- For the purpose 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.*”

- (iii) It is an established position of the law that if a discovery is made from a known compounds, a duty is cast upon the patent applicant to show that the discovery had resulted in the enhancement of a known efficacy of that substance [See *Novartis AG v. Union of India and others*, (2007), 4 MLJ 1153, page 15]. The Hon’ble Intellectual Property Appellate

Board has also held in *Novartis AG v. Union of India and Others*, IPAB, 26.06.2009, at pages 178 and 179, that “efficacy” in Sec. 3(d) means therapeutic efficacy.

- (iv) It is pertinent to note that the alleged Applicant has merely employed and substituted the known prior art elements/substituents/groups in the basic scaffold disclosed and taught in the prior art documents (**Exhibits A and B**) in order to arrive at the alleged invention. The prior art documents additionally teaches that the pyrimidine compounds disclosed therein inhibit ALK and are useful in the treatment of tumourous diseases and anti-cancer diseases which is also the subject matter of the alleged invention. From the teachings and disclosures in **Exhibits A to G**, it is apparent that one of skill in the art would have had a reasonable expectation of success in producing the compounds claimed in the impugned patent application retaining the identical backbone structure / basic scaffold as well as the activity of the compounds claimed therein.
- (v) It is further pertinent to note that the pyrimidine compounds/ phosphorous derivatives broadly claimed in the impugned patent application are structurally and functionally similar to the pyrimidine compounds/ phosphorous derivatives broadly claimed in the said prior art documents. Hence the Applicant is under the obligation to provide enhanced therapeutic efficacy data in comparison to the prior art products. The Applicant has conveniently not demonstrated enhanced therapeutic efficacy of all the claimed products in comparison to the prior art products. Hence the claimed compounds shall be considered to be the same substance and clearly falls within the ambit of Section 3(d) of the Act. The Opponent would like to bring to the kind attention of the Learned Controller that the the Supreme Court in its judgment in *Novartis vs. Union of India*, (2013) 6 SCC 1 held that a new form of known substance is outside the purview of the definition of “invention” if the said new form of a known substance does not pass the test of

efficacy required under Section 3(d) of the Act. The compounds claimed in the present Application are new form (derivative) of a known substance lacking enhanced therapeutic efficacy and hence cannot be regarded as non-patentable invention under Section 3, in view of disclosure in the prior art documents (**Exhibits A to G**).

- (vi) As stated in much detail above, the Applicant has failed to show any significant enhanced therapeutic efficacy with regard to the alleged invention claimed in the present Application.
- (vii) In view of the above, Claims 1 and 2 are liable to be rejected under Section 25(1)(f) read with Section 3(d) of the Act, being a derivative of a known substance lacking enhanced therapeutic efficacy.

**e. Section 25(1)(g): the complete specification does not sufficiently and clearly describe the invention.**

- (i) Section 25(1)(g) of the Patents Act provides a ground of opposition that the complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed.
- (ii) The Complete Specification accompanying the present Application discloses several compounds. The Applicant has now restricted the claims to a single compound, *brigatinib*.
- (iii) As stated above, Save for a few sweeping generalised statements regarding the activity of the claimed classes of compounds, the Complete Specification does not specifically disclose the potency of the claimed compound, *brigatinib*, for any kinase activity.
- (iv) Further, the Applicant is now advancing a completely new argument and new data to show that the claimed compound exhibits weaker InsR inhibition than TAE684, a previously known compound which is identified by the Applicant as the closest prior art. However, the Complete Specification is completely silent on this alleged effect of weaker InsR inhibition. It does not also identify it as a problem to be



solved. It is this activity that the Applicant is now canvassing as the advantage of the invention over the existing prior art.

- (v) Thus, the Complete Specification accompanying the present Application does not sufficiently and clearly describe the invention.
- (vi) For this reason the present Application ought to be rejected *in toto* under section 25(1)(g) of the Act.

37. It is submitted by the Opponent that all the above-mentioned prior art documents annexed to the present Pre-grant Opposition destroy the novelty of the alleged invention so claimed by the Applicant. The information in the prior art documents disclose the essential elements of the alleged invention. Novelty is destroyed when the essential elements have been disclosed, even if the details of executing the invention, or clear description of its properties or method of making it were not disclosed.

38. In *Enercon (India) Limited v. Aloys Wobben* ORA/6/2009/PT/CH, ORDER (No. 18 of 2013) the Intellectual Property Appellate Board of India noted that novelty may be denied on the basis of 'inherent anticipation'. It stated: "*the prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating prior art..... it is not necessary that inherent anticipation requires that a person of ordinary skill in the art at the time would have recognized the inherent disclosure. But it is necessary that the result is a necessary consequence of what was deliberately intended in the invention.*" Thus, the novelty in the present application is destroyed by all prior art documents cited herein.

39. It is further submitted that the inventive step claims in the present application are destroyed as what is claimed is obvious to a person skilled in the art, i.e. there is reasonable expectation of success embedded in the prior art which motivates a skilled person to arrive at the alleged claimed invention.

Obviousness cannot be avoided by showing some degree of unpredictability in the art, so long as there was a reasonable probability of success through disclosures provided in the prior art documents. Obviousness does not require absolute predictability of success. All that is required is reasonable expectation of success in the matter of pharmaceutical inventions. All the prior art documents annexed to this Opposition provide a reasonable predictability of success and the claimed compound is obvious to a person skilled in the art. Additionally, the claimed compounds do not involve a technical advance compared to existing knowledge.

40. The Opponent humbly submits that the prior art documents annexed to the present pre-grant opposition and also those cited in the FER demolish all the amended claims of the present Application, rendering the amended claims devoid of novelty, inventive step and obvious to a person skilled in the art. The Opponent states that grant of patents to the Applicant in other jurisdictions cannot tantamount to a grant of a patent in India. The Indian law is different from the laws in other jurisdictions and care has been taken by the law makers not to allow patents for pharmaceutical products that are not genuinely inventive or that are known earlier, or obvious to a person skilled in the art. The law specifically prohibits grant of patents for derivatives of known substances and also prevents abuse of the patent process by laying down grounds for opposition that prevent undeserving patents from being granted.
41. The Opponent states that the present Application No. 3939/KOLNP/2010 falls within the category of non-patentable inventions as described in Section 3(d) of the Patents act, and also does not meet the definition of “invention” and inventive step as set out in Section 2(1)(j) and 2(1)(ja) of the Act. The present Application ought to be rejected *in toto* under Section 25(1) read with clauses (j) and (ja) of section 2(1) and clause (d) of Section 3 of the Act.

**42. Prayers**

Having established non-patentability of the alleged invention and having adduced supporting evidence for each of the above grounds of Opposition, Opponent prays for the following reliefs:

- a. That the Applicant's Patent Application No. 3939/KOLNP/2010 having filed, with original claims as well as amended claims, be rejected *in toto* and the grant of Patent to the Applicant be refused.
- b. That the Opponent be granted leave to file further arguments and evidence against the impugned application.
- c. That copy of the reply of the Applicants and evidence, if any, be forwarded to the Opponent along with amendment to claims, if any;
- d. That the Opponent be granted leave to file response/rejoinder to the reply and the evidence of the Applicants.
- e. That the Opponent should be given an opportunity to oppose the amended claims, if any.
- f. That the Opponent be granted hearing in this case.
- g. That the Opponent be granted leave to refer to and rely upon full text of the documents referred to in this opposition.
- h. Such other and further relief/s be granted to the Opponent, as the Ld. Controller may deem fit in the facts and circumstances of this case.
- i. That the Opponent be awarded costs.

All communications relating to these proceedings may be sent to the following address in India:-

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**Dated this 10<sup>th</sup> day of July, 2017**



**Dr. GOPAKUMAR G. NAIR**

**Regn. No: IN/PA 509**

**(Agent for the Opponent)**

**Gopakumar Nair Associates**

To,

The Controller of Patents

The Patent Office

Kolkata