THE PATENTS ACT, 1970 (as amended)

and

THE PATENTS RULES, 2003 (as amended)

SECTION 43

In the matter of an application for a patent
Application No.201847020374
Dated 31/05/2018

Applicant **IONIS PHARMACEUTICALS, INC.**

Having address for service as Anand & Anand Advocates
B-41,Nizamuddin East
New Delhi – 110013, India

Agent- Devinder Singh Rawat (INPA-2554)

DECISION

1. An application for patent bearing number 201847020374 was filed at the Patent Office, Delhi on 31/05/2018. The request for examination was filed vide RQ No. R20194034551 dated 05/11/2019 under section 11B and rule 24B of the Patents Act, 1970 (as amended) and the Patents Rules, 2003 (as amended). The said application was published on 08/06/2018 with Journal number of publication 23/2018. The said application was examined under sections 12 and 13 of the Patents Act, 1970 (as amended) and the First Examination report (hereinafter referred to as FER) was issued on 15/06/2022. Thereafter, the applicant's agent submitted the reply to FER on 14/03/2023.

2. Following a review of the reply submitted by the applicant in response to the initial examination report and subsequent examiner's report, it was determined that the patent application was not in a condition suitable for granting. In accordance with the provisions of the Patents Act, 1970 (as amended), and to uphold principles of natural

justice for the applicant, a hearing was offered under Section 14 of The Patents Act, 1970. The hearing was scheduled for 22/02/2024, and the applicant's agent was duly notified of the outstanding objections via email dated 12/01/2024. Subsequently, the applicant filed adjournment requests twice, on 16/02/2024 and 19/03/2024. An extended hearing notice was generated on 21/03/2024 rescheduling the hearing to 22/04/2024. The hearing convened on 22/04/2024, and written submissions from the applicant's agent were received on 04/05/2024. Following a thorough review of the submissions, it was noted that objections raised in the hearing notice were successfully defended by the applicant and their agent. The objections discussed in the hearing include:

Objections

Formal Requirement(s)

1. Fees for 2 newly added claims (Rs 3,200) has to be paid

Invention u/s 2(1)(j)

The submissions in your letter dated 14/03/2023 have been considered carefully.However, following objections have been raised. Newly added claims 3-4 are not allowable u/s 59 of the Patents Act, 1970.As no amendment of an application for a patent or a complete specification or any document relating thereto shall be made except by way of disclaimer, correction or explanation, and in not in way of addition. Para 1 of FER is maintained as the applicant's reply is not satisfactory. The applicant in his correspondence argues that D1 teaches that ISIS 681257 was subcutaneously administered to 8-week-old female mice at 0.3, 1, 3, or 10mg/kg, but fails to provide any teaching or suggestion regarding an amount suitable for humans is not satisfactory.As, para [0175 and 0201- 0202] of D1 talks about that administered of a said compound is not limited to mice, but it also includes humans. Applicant's arguing that in examples 1 and 2 of the present application, a ≥ 30-fold improvement in potency in humans was observed for oligomeric compound ISIS 681257 in sterile saline solution is not satisfactory.As, the said examples does not clearly defined the said

improvement in the specification. Hence, by routine experimentation, the typical dose for humans can be arrived by a person skilled in the art in view of the cited documents. Hence there is no technical advancement over the cited documents and the inventive feature of the current invention is obvious to a person skilled in the art in view of the cited documents D1 to D2. Therefore, amended claims 1-2 and 5-13 do not involve inventive steps as required u/s 2[1(j)(a)] of the Patents Act, 1970.

Non-Patentability u/s 3

Para 2 of FER is maintained, As, the amended claims 1-2 and 5-13 are not patentable under section 3(e) as the composition claimed is is just an admixture of various ingredients without any demonstrated synergistic effect.

Sufficiency of Disclosure u/s 10 (4)

1. Para 3(I) of FER is maintained as the applicant's reply is not satisfactory for the amended claims 1-2 and 5-13 pertaining to a pharmaceutical composition are not enabled in the specification via working example. .Hence, these claims do not meet the requirement of 10(4) (b) of the Patents Act, 1970.

3. In the matter of the aforementioned proceeding, the applicant or their duly authorized patent agent, Devinder Singh Rawat (INPA-2554), appeared on behalf of the applicant and advocated in favor of the applicant's position. Following meticulous review of the submission presented by the applicant, the claims have been revised, and a novel set of claims (Claims 1-13) has been preferred. These claims exclusively pertain to o a pharmaceutical composition comprising ISIS 681257, or a pharmaceutically acceptable salt thereof, wherein the pharmaceutical composition contains from 75 mg to 85 mg of the oligomeric compound. Further the claims amended and restricted to enabled subject matter (working example 1 and clinical trial data), hence objection of sufficiency of disclosure has been waived off. For the formal requirement, prescribed fee has been paid for two newly added claims and hence this objection is also waived.

After considering the submission and data provided by the applicant, the subject matter of claims 1-13 can be considered inventive as optimizing the dose for antisense oligonucleotides (ASOs) was and is not routine. In particular, the development of the correct dosing of GalNAc conjugated ASOs in humans was not routine at the filing date: GalNAc conjugated ASOs are still a developing field of medicine to this date, and only recently the first GalNAc conjugated siRNA agents (not even an ASOs!) have been approved. Accordingly, an ordinarily skilled artisan has no past experience nor any literature available, at the time of filing of the present application to guide the development of the correct dosing amount for a GalNAc conjugated ASO.

Further, D1 provides no guidance to arrive at the specific dosage of 75 mg to 85 mg of ISIS 681257 in humans as claimed. Indeed, a dosage amount found suitable in mice may not directly correlate to a suitable regimen in humans. Accordingly, the ordinary skilled artisan would not have had a reasonable expectation of success in developing the specific claimed composition because doing so would have required excessive experimentation. D2 does not cure the deficiencies of D1. D2 merely teaches administering ISIS 494372 to a human at 100mg per day at days 1, 3, 5, 8, 15 and 22 for a total dose exposure of 600 mg over a 3-week period. See D2, at 1478. An ordinarily skilled artisan would not have had a reasonable expectation of success in developing the now claimed composition based on the teachings of D2. D2 only teaches administration of ISIS 494372.

In fact, D2 teaches away from a pharmaceutical composition comprising ISIS 681257, or a pharmaceutically acceptable salt thereof, for treating or preventing a disease or condition related to apolipoprotein(a) (apo(a)) and/or lipoprotein(a) (Lp(a)) in a human, wherein: (i) the treatment or prevention comprises administering from 75 mg to 85 mg of the oligomeric compound to the human during the a dosing period; and (ii) the dosing period is one month. Indeed, D2 teaches that a single dose of ISIS 494372 (50–400 mg) did not decrease Lp(a) concentrations at one month. See D2, at page 1478. An ordinarily skilled artisan looking to treat or prevent a disease by reducing the production of apo(a) in the liver and as a consequence, the level of Lp(a) lipoprotein in

blood would not expect from the teachings of D2 that a dosage less than 400 mg, let alone an amount from 75 mg to 85 mg as claimed, would decrease Lp(a) concentrations at one month.

The Applicant submits that a person skilled in art would not have had a reasonable expectation of success in developing the now claimed composition based on the teachings of D2 because D2 teaches that a significantly higher dose and more frequent dosing period than claimed would be expected to achieve efficacy with ISIS 494372, let alone with the structurally different compound, ISIS 681257. While D1 discloses that ISIS 681257 was more potent with a longer duration of action than ISIS 494372 in female mice, neither D1 nor D2 provide any teaching or suggestion of the surprising potency in humans. As shown in Examples 1 and 2 of the present application, a ≥ 30-fold improvement in potency in humans was observed for oligomeric compound ISIS 681257 in sterile saline solution. Indeed, an ordinarily skilled artisan considering D1 and D2 could not have predicted the unexpected ≥ 30-fold improvement observed in humans for ISIS 681257

In view of the above technical advantage over the cited prior arts D1-D2, subject matter considered to be inventive. Thus the objection of inventive step u/s 2(1)(ja) waived off. Further the objection under section 3(e) also considered to met as the antibody have advantageous efficacy over the known antibodies, hence objections raised under section 3 also considered to be met. Therefore, the subject matter in question does not fall within the ambit of section 2(1)(ja) and section 3(e). Regarding the objections raised under the header of sufficiency disclosure, the applicant has been filed the revised claims to define the terms and restrict the subject matter with disclosure made in complete specification and to the one invention. Therefore, the objections considered met, and the application is now being considered for grant.

4. Further, no pre-grant representation u/s 25(1) is found in the module.

5. Therefore, keeping in view the above facts, the written submission, instant application no. 201847020374 complies with the requirements of The Patents Act, 1970 (as amended). I, therefore, hereby order the grant of a patent with claim 1-13 filed in Document dated 04/05/2024, pages 10-11 of the document uploaded as "201847020374-Written submissions and relevant documents [04-05-2024(online)].pdf" in the e-module under the provisions of Section 43(1) of The Patents Act, 1970 (as amended).

6. This is to be noted that the aforesaid observations, and decision thereof, are based solely on the electronically uploaded documents to date.

Dated, 22 August 2024
(AKASH KUMAR)
Assistant Controller of Patents & Designs

……..End of The Document……