THROUGH E-FILING MODULE

Our Ref.: 28117/P-3 **March 14, 2023**

CONTROLLER OF PATENTS
THE PATENT OFFICE
DELHI

Re.: Indian Patent Application No.	**:**	**201847020374**
Date of Filing	**:**	**MAY 31, 2018**
Title of Invention	**:**	**MODULATING APOLIPOPROTEIN (A) EXPRESSION**
Applicant	**:**	**IONIS PHARMACEUTICALS, INC.**
Date of FER	**:**	**June 15, 2022**
Extension for 3 months filed	**:**	**December 9, 2022**
FER Due Date (Extended)	**:**	**March 15, 2023**
Controller in Charge	**:**	**Parvathy S**

RESPONSE TO FIRST EXAMINATION REPORT

Respected Madam,

Thank you very much for the first examination report dated June 15, 2022 in respect of the above application. The Applicant has filed an extension of three months to file response to the FER on December 9, 2022. A copy of the CBR has been enclosed.

Our submissions to the objections raised by the Learned Controller in the First Examination Report are as follows:

A. CLAIM AMENDMENT

Notwithstanding the foregoing/following, solely in the interest of expediting examination and in no way acquiescing to the validity of the Controller's rejection, we have revised the pending claims under the provisions of section 57(6) of the Patents Act.

All revisions have been made without prejudice to the possibility of future reinstatement of any excluded matter and/or subsequent filing of divisional applications based on any matter contained in the application as filed. Any amendments made by way of the present response, and

the observations contained herein, are made solely for the purposes of expediting the prosecution of this Indian patent application.

B. REPLY ON OBJECTIONS:

1) <u>Inventive Step</u>

The controller has alleged that the present invention lacks inventive step in view of the following documents:

- D1: US 2015/0126720 A1
- D2: SOTIRIOS TSIMIKAS ET AL: "Antisense therapy targeting apolipoprotein(a): a randomized. Double-blind. placebo-controlled phase 1 study". LANCET. vol. 386. no. 10002. Pages 1472-1483

The Applicant respectfully disagree with the opinion of the Learned Controller and submits that the presently amended claims are novel and inventive in view of the cited documents.

However, in an effort to expedite prosecution, please point out that the claims have been amended to recite, in relevant part, 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.

D1 does not teach or suggest a pharmaceutical composition according to the claims as amended. 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, let alone a pharmaceutical composition containing the specific dosage of 75 mg to 85 mg of ISIS 681257 as instantly claimed.

Moreover, an ordinarily skilled artisan would not have had a reasonable expectation of success in developing the now claimed composition for treatment at specific dosage amounts based on the teachings of D1. First, D1 only teaches doses suitable in mice. Second, D1 only teaches that ISIS 681257 was more potent with a longer duration of action than ISIS 494372 in female mice.

The Applicant respectfully submits that, contrary to the assertions of the Controller, 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. See e.g., GIVLAARI (givosiran). 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.

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.

As disclosed in D1, ISIS 494372, having different internucleoside linkages and nucleoside modifications and also lacking a GalNAc moiety, is a different oligomeric compound from ISIS 681257. See D1, at Example 89, Table 92. 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. Please point out that 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 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 light of these surprising results, when treating humans, ISIS 681257 and its salts can be administered at a significantly lower dose and/or less frequently than expected based on the earlier in vivo testing. Therefore, the presently claimed invention provides one or more improvements in treating humans including reduced cost of treatment, improved patient compliance, reduced

volume of administered medicinal product and/or potentially reduced risk of potential adverse events via lower dose administration regimens.

In the instant case, the claimed compositions and their results would be unpredictable based on the teachings of the prior art. Thus, Applicant submits that the claims are inventive over D1 and/or D2. Reconsideration and withdrawal of the rejection are requested.

In light of the above, the Applicant submits that the present invention is inventive and therefore reconsideration of the objection is requested.

2) <u>Non Patentability</u>

a) The Controller has alleged that the claims 1-112 fall within the scope of section 3(c) of the Indian Patent Act.

b) The Learned Controller has held that claims 113-150 and 154 are not patentable u/s 3(e) of the Patents Act 1970, as it is directed to a composition/method.

c) The Learned Controller has held that claims 151-152 are not patentable u/s 3(d) of the Patents Act, 1970 as the claimed sealed container/syringe is well known from the prior published documents.

d) The Learned Controller has held that claims 155 and 156 are not patentable u/s 3(i) of the Patents Act, 1970 as they claim for method of treatment.

e) The Learned Controller has held that claims 150 and 154 are not patentable u/s 3(n) of the Patents Act, 1970 as it claims for printed information.

The objection is moot in view of amended and therefore reconsideration of the objection is requested.

3) <u>SUFFICIENCY OF DISCLOSURE:</u>

- *The Learned Controller has held that claims 1-156 are broad and are not enabled in the specification via working examples in its whole breadth.*

The objection is moot in view of amended and therefore reconsideration of the objection is requested.

<u>Information of source and geographical origin of biological material used in the invention:</u>

- *The Learned Controller has held that source and geographical origin of the biological material used should be given in the specification in accordance with section 10(4)(d) of the Patents Act, 1970.*

The Applicant submits that the compound ISIS 681257 is not naturally occurring and is synthesized chemically.

In view of the above reconsideration of the objection is requested.

4) **SCOPE:**

- *The Learned Controller has held that claims 1-156 do not meet the requirements of section 10(4)(c) of Patents Act, 1970 as the claim is defined in terms of the achievable end effect.*

The objection is moot in view of amended and therefore reconsideration of the objection is requested.

5) **CLARITY AND CONCISENESS:**

- The Learned Controller has held that claims 1-156 do not meet the requirement of section 10(5) of Patents Act, 1970 as the phrases like "comprises", "comprising", "one or more", "at least", "optionally", "no more than", "not less than" which makes the claim too broad, unclear and vague as it represents an optional feature with no limiting effect, thus introducing ambiguity on the scope of the claim.
- The Learned Controller has held that claim 1 does not meet the requirement of section 10(5) of Patents Act, 1970 as the term ISIS 681257 is an internal designation and not widely recognized in the art. The claims have to be clear per se without any need to refer to the description. In the absence of the explicit indication of the nucleotide sequence and the modifications of the compound, the scope of claim 1 is not clear

The objection is moot in view of amended. Further, claims have been amended to define the oligomeric compound by its chemical structure.

In view of the above reconsideration of the objection is requested.

6) **DEFINITIVENESS:**

The Learned Controller has held that claims 149, 155 and 156 do not meet the requirement of section 10(4)(a) of Patents Act, 1970 as the claimed method is not well defined with its corresponding process steps.

The objection is moot in view of amended and therefore reconsideration of the objection is requested.

7) **OTHERS REQUIREMENTS:**

The Learned Controller has held that Claim 157 claiming for the use is not an invention within the meaning u/s 2(1)(j) of the Patents Act, 1970.

The objection is moot in view of amended and therefore reconsideration of the objection is requested.

PART-III: FORMAL REQUIREMENTS

Statement & Under Taking (Form 3 Details):

- We have filed details of the corresponding foreign patent applications vide our letter dated December 9, 2022. Copy of the same is enclosed herewith.

- We have filed search and examination reports in respect of corresponding Australian, Brazilian, Chile, Chinese, Colombia, European, Isreal, Japanese and US application. Copy of the letter dated December 9, 2022 with CBR is enclosed herewith.

  In view of the above reconsideration of the objection is requested.

In view of our submissions and amendments, we request to the Learned Controller to kindly allow the application to proceed for grant before the expiry of extended due date i.e., **March 15, 2023.** We also wish to submit that all objections have been complied herewith and information as required under Section 8 of the Act has been submitted at the Indian Patent Office.

However, considering there is no advance intimation as to the date of grant of the patent application, we request the learned Controller to kindly advise us of any further information required under Section 8(1) and/or 8(2) after the expiry of the above mentioned due date.

In case of any adverse decision in respect of the pending application, we request the learned Controller to kindly provide us an opportunity of being heard under Section 14 before the final disposal of the matter.

Yours faithfully,

Devinder Singh Rawat
IN/PA No. 2594
Of Anand And Anand Advocates
Attorney for the applicant

Encl.:

- Revised claims (Marked up and clean copy)
- Copy of Form 3 filed on December 9, 2022
- Copy of letter dated December 9, 2022 with CBR filing search and examination reports.