

CLAIM NOS: HP-2017-000040, HP-2017-000069 and IL-2017-000016

IN THE HIGH COURT OF JUSTICE

CHANCERY DIVISION

PATENTS COURT

B E T W E E N:

(1) SILENCE THERAPEUTICS GmbH

Claimant in the SPC action /

Defendant in the revocation action

(2) SILENCE THERAPEUTICS PLC

Defendant in the revocation action

- and -

(1) ALNYLAM UK LIMITED

(2) ALNYLAM PHARMACEUTICALS INC

(3) THE MEDICINES COMPANY UK LIMITED

Defendants in the SPC action /

Claimants in the revocation actions

DEFENDANTS' SKELETON ARGUMENT FOR THE CMC

(Hearing estimated at 2 – 3 hours)

Mark Chacksfield

Michael Conway

Instructed by Potter Clarkson LLP for the First and Second Defendants

and

Bird & Bird LLP for the Third Defendant

*Suggested pre-reading
(estimate 2 hours)*

The Patent (*skim for flavour*) [A1]

Pleadings – Silence’s SPC declaratory action

Particulars of Claim [B1/2]

Alnylam’s Defence [B1/4]

[TMC’s materially similar Defence is at [B1/5] but need not be read separately]

Alnylam’s revocation action & Silence’s infringement counterclaim

Particulars of Claim [B1/8]

Grounds of Invalidity [B1/11]

(the prior art need not be read, but for reference is in [B2, parts 1 & 2])

Defence and Counterclaim [B1/12]

Reply and Defence to Counterclaim [B1/13]

*[Note also the materially parallel **TMC’s revocation action & Silence’s infringement counterclaim** are at [B1/14 – 18] but need not be considered separately.]*

Evidence

Morgan 2 [C1/5]

Nicholas McDonald 2 [D1/7]

Morag Macdonald 2 [D2/4]

Morag Macdonald 3 [D2/9]

Excerpt from Alnylam’s EPO opposition [attached hereto]

Draft consolidated order (with opposing positions marked up) and clean version [D2/10]

Introduction and issues

1. This is the CMC in a patent action concerning so-called RNA interference (‘RNAi’). The patent in suit (EP (UK) 2,258,847, ‘the Patent’) is a relatively recently granted divisional patent based on a filing in 2003, nearly 15 years ago.
2. The Patent is under opposition, the 9 month window having recently closed. There were also earlier opposition proceedings against the grandparent patent (EP 1,527,176), during which Silence was forced to abandon its initially broad claims and amend down to a very restricted narrow set of features which are not said to be of any commercial relevance.
3. Finally there is the parent patent (EP 1,857,547, the ‘Parent’) in relation to which the EPO has recently issued a decision to grant. So far Silence has refused to state its intentions with respect to this patent.

4. Used as a therapy, RNAi, in a nutshell, involves taking a chunk of modified RNA and introducing it into a patient, where it interferes with expression of specific undesirable proteins. It is a complex and relatively new field, based upon observations in nematode worms reported in *Nature* in 1999 and was the subject of the 2006 Nobel Prize for Medicine. It is not, to our knowledge, a technology that has previously been before the Court.
5. **Silence** is a smallish biotech company. Silence describes itself as a '*leader in the discovery, delivery and development of novel RNA therapeutics for the treatment of serious diseases with unmet medical needs*' and states that '*[its] fundamental chemical modification technology is a core foundational innovation for today's RNAi sector*'¹. Despite the passage of 15 years since the priority date of its allegedly foundational Patent, Silence does not have any RNAi projects of its own which have successfully progressed beyond early pre-clinical work². It is apparently in the light of these difficulties that Silence has sought to develop a business model as a patent assertion entity, which is the focus of these proceedings.
6. **Alnylam**³ is a larger US-based biotech company which has extensively developed RNAi technology and, as can be seen from the evidence, has invested heavily in R&D directed to developing RNAi into actual therapeutic candidates including an extensive programme of clinical trials (see Nicholas McDonald 1 & 2).
7. **The Medicines Company** ('TMC'), in collaboration with Alnylam, has also been developing RNAi therapeutic products as a class of medicines and in particular 'inclisiran'. TMC has made and is continuing to make a substantial investment in developing inclisiran (see witness statements of Morag Macdonald 1 & 2).
8. The action involves three claims:
 - i. The first is a very unusual type of claim for declaratory relief of a kind never previously brought in the UK nor elsewhere⁴. Silence seeks a declaration that it would be entitled to SPCs for the Patent based on Alnylam's and TMC's as yet un-granted (and save in respect of patisiran, yet to be applied for) marketing

¹ Morag Macdonald 2 §19.

² Morag Macdonald 2 §19.

³ For the purposes of this CMC (but without any admission on issues of substance), there is no need to distinguish between the two Alnylam entities.

⁴ To our knowledge, at least.

authorisations, on the footing that it says that it wants to claim licence fees for the SPC period⁵ ('the SPC Declaration Action');

- ii. The second and third are claims for the revocation of the Patent and declarations of non-infringement, respectively by Alnylam and TMC, wherein Silence has brought counterclaims for infringement ('the Patent Actions').
9. The SPC Declaration Action was issued in July 2017. At Silence's insistence, and upon its application, the three actions have already been set down to be heard from the first available date on or after 3 December 2018. The trial is estimated to require 10 days of Court time, and additionally 2 days of pre-reading. The technical difficulty rating is agreed to be 5.
10. The claims are each valued at in excess of £10M, and the products themselves are predicted by third party analysts to achieve total sales until the end of 2028 (the date when any SPC will expire) of around \$60 billion⁶. Silence has previously stated that its claims for royalties could reach "*hundreds of millions of pounds*"⁷. On any basis this is amongst the very heaviest of biotech litigation.

The Products

11. There are four different products in issue at different stages of development. Each of them has the potential to offer important therapies to patients in areas of unmet or insufficiently met clinical need:
- i. **Patisiran** is an investigational RNAi therapeutic targeting transthyretin (TTR) in development for the treatment of hereditary ATTR amyloidosis (hATTR amyloidosis) – a genetic disease affecting approximately 50,000 patients worldwide, with limited treatment options.
 - ii. **Fitusiran** is an investigational RNAi therapeutic targeting antithrombin (AT) in development for the treatment of haemophilia and rare bleeding disorders.
 - iii. **Givosiran** is an investigational RNAi therapeutic targeting aminolevulinic acid synthase 1 (ALAS1) for the treatment of acute hepatic porphyrias (AHPs).

⁵ More particularly that the four products are protected by the Patent within the meaning of Art 3(a) of the SPC Regulation, and that any MA granted would be a valid authorisation within the meaning of Art 3(b).

⁶ Nicholas McDonald 2 §8.

⁷ [B1/9].

- iv. **Inclisiran** is an investigational RNAi therapeutic being developed by TMC for the treatment of hypercholesterolemia.

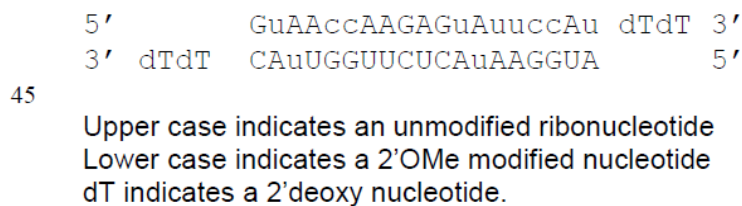
Issues in the case

12. The claims are at p.110-111 of the Patent [A1]. Claims 1 – 6, 8 – 10 and 13 of the Patent are asserted. Claim 1 reads:

10 **Claims**

1. A ribonucleic acid suitable for mediating RNA interference comprising a double stranded structure, whereby the double- stranded structure comprises a first strand and a second strand, whereby the first strand comprises a first stretch of contiguous nucleotides and whereby said first stretch is at least partially complementary to a target nucleic acid, and the second strand comprises a second stretch of contiguous nucleotides and whereby said second stretch is at least partially identical to the target nucleic acid,
15 **characterised in that**
said first strand and said second strand comprises a plurality of groups of modified nucleotides having a modification at the 2'-position whereby within the strand each group of modified nucleotides is flanked on one or both sides by
20 a flanking group of nucleotides whereby the flanking nucleotide(s) forming the flanking group of nucleotides is/are either an unmodified nucleotide(s) or a nucleotide(s) having a modification different from the modification of the modified nucleotides,
the first strand or first stretch and the second strand or second stretch form a pattern of modified nucleotides, wherein groups of modified nucleotides are alternating with flanking groups of nucleotides and
25 the pattern of modified nucleotides of said first strand is the same as the pattern of modified nucleotides of said second strand.

13. Infringement is disputed, and the basis for Silence's assertion of infringement is far from clear and to date has not been explained. For example, the structure of patisiran (likely the first of the products to obtain an MA) is set out in Alnylam's opposition to the Patent as follows:



14. It is admitted that not all of the claims are entitled to priority, and validity is attacked for lack of novelty, obviousness and insufficiency.
15. The insufficiency plea is of particular relevance to the issues on this CMC, and the Court is invited to read sections 9.2 – 9.4 of Alnylam's Notice of Opposition to the Patent [attached hereto], which are directed to scope of claim under obviousness in the *AgrEvo* sense (Art 56) and insufficiency (Art 83) for a flavour of some of the arguments.
16. There are additionally issues arising out of Silence's claim to declaratory relief, and as to the meaning and scope of Arts 3(a) and 3(b) of the SPC Regulation.

The Issues on the CMC

17. Subject to the Court's approval of the agreed provisions, the following matters remain in issue:
- i. Disclosure in relation to insufficiency;
 - ii. Deadlines for fact evidence;
 - iii. The number of expert witnesses;
 - iv. Clarification of Silence's position on the Parent Patent;
 - v. A few remaining disputes on the dates for specific steps.

Disclosure

18. The parties have filed disclosure statements [B1/6, 21, and 22]. That of Silence is directed only to its SPC claim, and not to the Patent Actions.
19. The parties are agreed that Alnylam and TMC should between them provide product descriptions addressed to the four products.
20. No disclosure is sought as regards obviousness. The issue between the parties concerns disclosure relating to insufficiency.
21. This is a case in which insufficiency is, as the Court will appreciate from the pleadings and the gist of the opposition submissions, a substantive and substantial one – it is not just a 'sheep dog' as is sometimes the case. The allegation that the teaching of the Patent is not sufficient to support claims of the breadth that Silence appears to advance is plainly a real one which will require serious investigation at trial, and one of the core issues is this: do the oligonucleotides as parameterised within the claims actually work?
22. This raises a straight issue of fact – which of the modified oligonucleotides are stable and effective? That is something that is likely not readily answerable from the published papers, since rarely if ever do companies publicise failures, but it is material that the parties have in their possession which can readily be produced⁸.
23. Alnylam and TMC, in the course of R&D work, have between them made and tested many different modified potential RNAi products, in the course of which testing they have

⁸ Morag Macdonald 3 §5.

encountered many difficulties, failures and dead end potential products. The identification of the oligonucleotides tested, and the results of the tests performed on them, is highly relevant to the question of whether and to what extent the claims encompass inoperative subject matter⁹.

24. Alnylam and TMC intend to adduce fact evidence at trial about this, and, if ordered, to provide the appropriate disclosure.
25. Mr Morgan questions whether the disclosure from Silence would be useful¹⁰. But given its 15 years of work, without any real progress, the inference is that Silence has carried out research into a variety of RNAi therapeutic targets and presumably researched the modification of a range of siRNAs for this purpose which have not in fact proved stable and efficacious, despite their knowledge at least of what is disclosed in the Patent¹¹.
26. Alnylam and TMC have written to Silence requesting that it clarify whether or not it proposes to advance any positive case at trial on insufficiency based upon or by reference to any RNAi molecules produced or tested by it or its licensees (whether developed in factual evidence, via expert evidence or through materials or questions put to any witness at trial)¹². This is a letter to which Silence has failed to respond, despite being chased.
27. One can understand, tactically, why Silence refuses to do so. It wishes to keep open the option of adducing such evidence without stating this now, since stating this now would have obvious disclosure ramifications.
28. Silence should not, however, be allowed to duck the issue in this way, and should make clear at the CMC whether or not it will advance any such case at trial. If it will not make its position plain, then a timetable for it to do so should be provided, as per paragraph 9.2 of Alnylam and TMC's updated draft order (see Exhibit MXM-7 to Morag Macdonald 3).

⁹ Or, if said to be functionally limited, are clearly defined.

¹⁰ Morgan 2 §§16-19.

¹¹ Morag Macdonald 2 §32. The Defendants' position in this regard is also supported by the learned editors of Terrell, who state that *"In contrast to the position on obviousness, disclosure going to pleaded insufficiency allegations is generally more readily ordered. It can be powerful evidence in support of an insufficiency if the patentee's own documents show that despite serious efforts to do so, they were unable to work the claimed invention, either at all or in some material respect. Similarly, attempts of the party alleging insufficiency will be equally relevant."* – Terrell on Law of Patents, (18th Edn. Sweet & Maxwell 2016) at 19-295.

¹² Morag Macdonald 3 §8.

29. If Silence chooses not to run a case based upon or by reference to its (or its licensees) work, then Alnylam and TMC are more sanguine about the disclosure issue, and will not press for it¹³.
30. If, however, Silence is to run such a case then it should give appropriate disclosure. The question is then just one of what is appropriate, in all the circumstances¹⁴.
31. This is of course a case of the highest value, and complexity. Third parties put the total aggregate sales up to 2028¹⁵ of the four products in the region of **\$60 billion**. Silence has proclaimed that it seeks royalties in the “*hundreds of millions*”, and whilst it will no doubt seek to retreat from those figures at the hearing by reference to the local nature of this action, the reality is that it is trying to use this jurisdiction as a testing bed for the totality of its royalty claim.
32. It is also an action with a wider public interest, relating as it does not only to a public monopoly right, but a monopoly right which Silence has threatened to try to use to prevent the marketing by Alnylam and TMC of the four products¹⁶, each of which is directed to treating areas of unmet or insufficiently met clinical need.
33. Mr Morgan’s evidence is that the disclosure exercise would be expensive. He quotes a figure of £1.5M, although the explanation of this in his evidence is most unclear. Given that this figure is 10 times the costs anticipated by Alnylam, a company which is substantially larger and which has successfully taken four products into advanced stages of development, one would have expected a much more detailed explanation to support these figures.
34. Furthermore Ms Macdonald is surprised by these numbers, and in her experience puts the normal costs of a disclosure search even of the scope described at about a fifth of that figure. She does not understand why this exercise would cost the sorts of sums that Mr Morgan suggests, and he does not provide any detail to explain the figures he advances. See Macdonald 3 §§10 – 12 [D2/9].
35. Lastly Mr Morgan notably fails to make any counter suggestion that would be, in his view, proportionate to the matters which are in issue in this case; a case which Silence seeks to

¹³ Reserving their rights to draw inferences in due course.

¹⁴ CPR 31.5(7) and the overriding objective are germane here, in particular so as to achieve justice between the parties having regard *inter alia* to the value and importance of the case to the parties, equality of arms, the relevance of the documents sought and the costs of the exercise.

¹⁵ The end of any potential SPC period.

¹⁶ E.g. Morgan 1 §30 [C1/1].

use to extract royalties it puts in the hundreds of millions. Where a party brings a case to Court, and intends to rely on its own internal work to support it, it is not good enough for it just to say “the disclosure you propose is too much so you can’t have anything”. Only Silence has knowledge of the nature of the documents in its possession after all¹⁷. In particular it is not clear whether all of the potential documents he refers to actually relate to the core issue of the identities of modified oligonucleotides tested for stability and efficacy in vitro and in vivo, and the results of those tests, nor does he indicate a different search that would capture the relevant material in a more cost-effective manner.

36. As regards the suggestion of a PDD, this was proposed so as to facilitate the parties’, and the Court’s, understanding of the documents disclosed. The proposal was purely a practical one, intended to reduce costs overall. Given Mr Morgan’s suggestion that the costs of this would extend to £3M (a figure that, we submit, indicates more about Silence’s approach to estimating costs than anything else), then Alnylam and TMC are not going to press the point.
37. As regards the SPC claim, both sides may wish to adduce fact evidence relating to the pleaded issues, but are content to progress this part of the case without disclosure on either side.

Deadlines for fact evidence and CEA notices

38. There is a dispute over the deadline for the parties to serve fact evidence. Silence seeks a date in line with the expert evidence: 14 September 2018 for evidence in chief and replies on 26 October 2018. Alnylam and TMC consider this unworkable. It is likely that substantial aspects of the fact evidence will be material to which the experts will need to have reference when preparing their reports – insufficiency for example. Fact evidence therefore needs to come properly in advance of the expert reports.
39. The only reason Silence has given for its proposed dates is the inconvenience that it says would be involved in requiring the parties to serve fact evidence during the summer vacation period.¹⁸ As it is, however, Alnylam and TMC now propose that fact evidence be exchanged on 31 May for evidence in chief and 28 June for any reply evidence. These dates are suggested to ensure that there is proper time between the service of fact and expert evidence, but have the happy coincidence of dealing with Mr Morgan’s summer vacation point.

¹⁷ And this is not helped by Silence’s failure to provide a disclosure report relating to the Patent Actions.

¹⁸ Morgan 2 §38.

40. CEA notices should be filed with fact evidence in chief, since after all that is what they are.

The number of expert witnesses

41. The Patent relates to the therapeutic use of modified oligonucleotides in RNAi. Alnylam and TMC wish to call two experts (they agree that it is appropriate for them to share experts): one in RNAi technology and one in oligonucleotide therapeutics, reflecting the underlying issues.
42. Silence disagrees and says that only one expert witness is necessary on each side, in the field of oligonucleotide therapeutics.
43. The evidence of Ms Macdonald, based on her investigations of the field to date, is that typically no one individual is expert in both the chemistry relating to oligonucleotides and the therapeutic application of RNA interference technology. As such Silence's proposal is unrealistic or unworkable.
44. Mr Morgan cites the increased costs of having two experts, but that must be considered in the context of litigation of this value and complexity. As Ms Macdonald notes in her evidence, it is not uncommon that more than one expert will be instructed in biopharmaceutical cases involving issues of both the underlying science and therapeutic application¹⁹, and there is a need for such here.

Clarification of Silence's position on the Parent Patent

45. Shortly before Christmas the EPO issued a decision to grant the Parent Patent. The expected date for mention of the grant is 17 January 2018. The Defendants have separately written to Silence requesting that it state its intentions in relation to the Parent Patent. It must know its plans, since this patent has been 15 years in the writing, and no doubt has been crafted with its patent assertion business in mind. But thus far Silence has failed to respond substantively.²⁰
46. The Parent Patent and the Patent derive from the same application, and are very closely related. If Silence intends to make any claim in respect of the Parent Patent, whether for infringement and/or for some kind of declaratory relief (if available), then it is self-evidently desirable that it should do so within the present proceedings.

¹⁹ Macdonald 2 §38.

²⁰ CMS second letter of 8 January 2017.

47. It would have been helpful had Silence chosen to indicate its intentions in advance of the CMC, but its position has instead been tactical and remains unknown²¹. This game playing should stop, and if it is not willing to break its silence at the CMC then Silence should be required to state its position within a reasonable period thereafter – by 28 February 2018 is proposed.

Miscellaneous dates

48. There are a number of other dates on which the parties have yet to agree, namely:
- i. Notices to Admit Facts;
 - ii. Notification of independently valid claims;
 - iii. Date for nominating experts;
 - iv. Service of expert reports in chief and in reply.
49. The first two have a little substance. Silence proposes 1 June and 13 April 2018 respectively. These are too late. In general, and in litigation of this weight in particular, the parties should deal with matters promptly and up front. This is litigation of Silence's bringing, and it is they who forced an early application for a trial date on Alnylam and TMC. There is no reason to delay getting on with matters. Alnylam and TMC suggest 14 February 2018 and 28 February 2018 respectively.
50. The remaining dates appear minor points, which it is hoped can be agreed, and if not should not take long to address orally.

²¹ See CMS' second letter of 8 January 2017.