Intellectual Property Office

BL O/0772/23

11 August 2023

**PATENTS ACT 1977**

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| APPLICANT | Hugh Robert Wotherspoon |
| ISSUE | Whether patent application GB 1812182.2 complies with the requirements of sections 1(1)(b), 14(3) and 14(5)(c) |
| HEARING OFFICER | Dr L Cullen |

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**DECISION**

**Introduction**

1 Patent application GB 1812182.2 ("the application") entitled "IL-1β antibody" was filed on 25 July 2018 in the name of "Hugh Robert Wotherspoon" ("the applicant"). The application was published on 29 January 2020 as GB 2575853 A. The period for putting this application in order under Section 20 of the Patents Act 1977 ("the Act") has been extended as-of-right under rule 108(2) of the Patents Rules 2007 ("the Rules") and extended thereafter under rule 108(3) to 25 July 2023.

2 The first examination report was issued by the examiner, as a combined search and examination, on 27 February 2019, raising objections under inventive step (Section 1(1)(c) of the Act), sufficiency (Section 14(3)), support (Section 14(5)(c)) and clarity (Section 14(5(d)). The applicant responded with arguments and without amendment to the application in a letter dated 3 February 2020, leading to a further examination report dated 10 June 2022, where the examiner maintained their support and sufficiency arguments, with a warning that they may raise a 'squeeze' inventive step argument at a later date. A further response from the applicant dated 26 July with further arguments and no amendments prompted the examiner to issue a pre-hearing report on 6 December 2022, offering the applicant a hearing. The issues to be addressed at the hearing were identified as sufficiency, support and inventive step.

3 After some unavoidable delays, the matter came before me at a hearing conducted by telephone on 18 May 2023. As I noted above, the unresolved issues to be addressed were sufficiency, support and inventive step as set down in the pre-hearing report of 6 December 2022. I thank Mr Wotherspoon for his detailed skeleton arguments provided in his letter dated 5 January 2023 and his email of 8 May 2023.

4 The applicant represented himself at the hearing. Dr Rowena Dinham acted as an assistant to the Hearing Officer on this case. The examiner, Dr Graham Feeney, was also present at the hearing.

**The Invention**

5 The invention relates to the second medical use of a known anti-IL-1β antibody to reduce the risk of an event of acute pancreatitis in a patient who has had a prior event of acute pancreatitis. Pancreatitis is an inflammation of the pancreas, with two main types: chronic and acute. As suggested by the different terminology, and as pointed out by Mr Wotherspoon at the hearing, these are two distinct conditions with distinct symptoms, i.e.:

- chronic pancreatitis (CP) is a long-term condition where the pancreas starts to fail due to damage leading to scarring which interrupts its function.

- acute pancreatitis (AP) may resolve within a few days; the most common causes are gallstones and alcohol use, and hence the physician treating AP will eliminate alcohol use or gallstones as a cause in the first instance. While the symptoms of AP may resolve within a few days, it can recur. If continuing bouts of AP recur, it may damage the pancreas to an extent that it develops into chronic pancreatitis.

6 Interleukin IL-1β is a pro-inflammatory cytokine, and the invention suggests that inhibition of this by the administration of an anti-IL-1β antibody will reduce the bile/ pancreatic duct vessel wall inflammation associated with non-alcohol related, non-gallstone related recurring AP.

7 The application itself has some detail surrounding the effects of the anti-IL-1β antibody, canakinumab, in the modulation of the levels of IL-1β and provides examples in the form of prior art disclosures of the treatment of gout and type 2 diabetes mellitus (Figures 2 and 3, respectively). Also provided is prior art data demonstrating the effects of canakinumab on levels of the clinical marker of inflammation, human C-reactive protein (CRP), during a type 2 diabetes treatment trial.

8 I note that none of the experimental data provided in the application is new, and that none of this experimental evidence demonstrates that inhibition of IL-1β would be an effective treatment for AP. I will return to expand this point further in the analysis below.

**The Claims**

9 There are 16 claims, with claim 1 being the only independent claim. As no amendments have been made during the examination process, the claims are as filed with the application on 25 July 2018. This single independent claim reads as follows:

1. *An IL-1$\beta$ binding antibody or functional fragment thereof for use in reducing the risk of having an event of acute pancreatitis in a patient who has had a prior event of acute pancreatitis*.

Dependent claims 2-16 define details of the antibody itself and how it can be administered.

**The Issues to be decided**

10 There are three issues to be decided in this case:

(i) Does the specification as filed disclose the invention in a manner that is clear and complete enough for it to be performed by a person skilled in the art?

(ii) Are the claims supported by the description as filed?;

(iii) Do the claims involve an inventive step?

I will first consider sufficiency and support before moving to consider inventive step.

## Sufficiency under Section 14(3) and Support under Section 14(5)(c)

**The Relevant Law**

11 Section 14 of the Act, entitled 'Making of Application', refers to certain requirements that the specification and its associated claims must meet to be allowable. In the present case we are concerned with Sections 14(3) and 14(5)(c).

***Section 14(3) - Sufficiency***

12 Section 14(3) of the Act relates to the specification and reads as follows:

> *The specification of an application shall disclose the invention in a manner which is clear enough and complete enough for the invention to be performed by a person skilled in the art.*

13 As set down in section 130(7) of the Act, section 14(3) is intended to have, as nearly as practicable, the same effect as the corresponding provisions of the European Patent Convention (EPC) and the Patent Cooperation Treaty (PCT). Article 83 EPC and Article 5 PCT require the invention to be disclosed "*in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art*". An objection under this section of the Act is often referred to as "sufficiency of disclosure" or "sufficiency". This pre-grant provision concerning the patent application accords directly with section 72(1)(c) of the Act which sets out the same requirement for the validity of the granted patent. Thus, while much of the case law relating to sufficiency derives from proceedings concerning granted patents under section 72, the principles set out in these cases are pertinent to section 14(3). It is the responsibility of the applicant to

ensure that, at the time of filing the application, the disclosure is clear enough and complete enough in respect of the invention defined in each of the claims. If it is not, then the application shall be refused or, if it is possible to do so, the claims must be restricted or amended to that matter which has been adequately disclosed, i.e., that for which there is an enabling disclosure. Deficiencies in the disclosure cannot be corrected subsequently by adding matter because of the prohibition under section 76(2) of the Act.

14 The overall purpose of section 14(3) is to prevent the patent applicant from claiming products or processes which the teaching of the specification does not enable the skilled person to perform. In effect, one is being asked to determine if there is enough information in the specification as filed by the applicant, to allow the person who has a reasonable knowledge and understanding of the technical area described, to carry out the invention defined in the claims.

15 Kitchin J provided a summary of the relevant principles to be applied when assessing sufficiency (at paragraph 239) in *Eli Lilly*[1]:

> *"The specification must disclose the invention clearly and completely enough for it to be performed by a person skilled in the art. The key elements of this requirement which bear on the present case are these:*
>
> *(i) the first step is to identify the invention and that is to be done by reading and construing the claims;*
>
> *(ii) in the case of a product claim that means making or otherwise obtaining the product;*
>
> *(iii) in the case of a process claim, it means working the process;*
>
> *(iv) the sufficiency of the disclosure must be assessed on the basis of the specification as a whole including the description and the claims;*
>
> *(v) the disclosure is aimed at the skilled person who may use his common general knowledge to supplement the information contained in the specification;*
>
> *(vi) the specification must be sufficient to allow the invention to be performed over the whole scope of the claim;*
>
> *(vii) the specification must be sufficient to allow the invention to be so performed without undue burden."*

[1] *Eli Lilly v Human Genome Sciences*, [2008] RPC 29

16 The claims are interpreted in the light of the description and the drawings as set out in section 125 of the Act. They are construed in a purposive manner following the established principles of UK patent law[2].

17 For the purposes of section 14(3), the skilled person is seeking to make the patent work and does so with the common general knowledge at the time the patent was filed. The skilled worker has the patent in front of them, and thus is "*trying to carry out the invention and achieve success, ... not searching for a solution in ignorance of it*." (see *Zipher*[3] at page 50).

18 As noted by Lord Hoffman in the House of Lords decision in *Kirin-Amgen*[4]:

> "*Whether the specification is sufficient or not is highly sensitive to the nature of the invention. The first step is to identify the invention and decide what it claims to enable the skilled man to do. Then one can ask whether the specification enables him to do it."*

19 Whilst there is only one provision under the Act, it is well established in UK law that the understanding of what sufficiency is - in terms of the disclosure being clear and complete enough for the invention to be performed by the person skilled in the art - can be approached in three different ways, i.e.:

(i) Classical insufficiency
(ii) Insufficiency by uncertainty/ambiguity
(iii) Insufficiency by excessive claim breadth

In this instance, the examiner considers the disclosure to be insufficient by classical insufficiency, which relates to the situation where there is no enabling disclosure. This has been usefully summarised by Floyd J in *Zipher*[3]:

> *"Classical insufficiency arises where the express teaching of the patent does not enable the skilled addressee to perform the invention. This type of insufficiency requires an assessment …of the steps to which it would be necessary for the skilled reader or team to take in following the teaching of the specification and in order to arrive within the claim. Plainly the steps should not include inventive ones. But a patent can also be found insufficient if the steps can be characterised as prolonged research, enquiry or experiment."*

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[2] The Manual of Patent Practice explains the IPO's practice under the Act and Rules and makes helpful references to relevant case law. In this instance, see Section 14, particularly paragraphs 14.115-14.116.1 (at Manual of Patent Practice - Section 14: The application - Guidance - GOV.UK (www.gov.uk))

[3] *Zipher Ltd v Markem Systems Ltd.*, [2009] FSR 1

[4] *Kirin-Amgen Inc v Hoechst Marion Roussel* [2005] RPC 9

*Sufficiency of second medical use claims*

20 The present case relates to a new therapeutic use, referred to as a second medical use claim, which is a purpose-limited product claim which can confer novelty for a new specific medical use of a known compound.

21 The question of what is necessary to render an application or patent relating to a second medical use sufficient was discussed by the Supreme Court in *Warner-Lambert*[5]. In its decision, the Court considered a number of principles that can be used to assess the sufficiency of medical use claims. The claims of interest in *Warner-Lambert* were in the Swiss format, but the principles outlined apply equally to the new form of medical use claims which have replaced Swiss claims following the amendments to the EPC in 2000 and which have been given effect in Section 4A of the Act. In the present case we are dealing with a claim in the new form, *i.e.*, the post-EPC 2000 format.

22 The sufficiency requirement in law establishes an underlying principle to prohibit claims that exceed the disclosed contribution to the art. The purpose of the plausibility requirement is essentially to prevent '*armchair inventors*', who make speculative claims but who have '*not done anything new or inventive at all but have simply sought to patent abstract possibilities'*, and it is one element that can be used in the test for sufficiency.

23 As part of its judgment, the court in *Warner-Lambert* outlined, in paragraphs 36 and 37, how the concept of plausibility applies to the statutory requirement for sufficiency. Considering the earlier Court of Appeal judgment in this case, the Supreme Court found that there is a general principle for determining if a claim to a medical use is plausible. The court set this down as follows (my emphasis added in bold):

> *"36. The Court of Appeal's statement of the effect of the plausibility test has already been quoted (para 20 above). They considered that the threshold was not only low, but that the test could be satisfied by a "prediction … based on the slimmest of evidence" or one based on material which was "manifestly incomplete". Consistently with that approach, they considered (paras 40, 130) that the Board's observations in SALK laid down no general principle. I respectfully disagree. The principle is that the specification must disclose some reason for supposing that the implied assertion of efficacy in the claim is true.* ***Plausibility is not a distinct condition of validity with a life of its own, but a standard against which that must be demonstrated. Its adoption is a mitigation of the principle in favour of patentability. It reflects the practical difficulty of demonstrating therapeutic efficacy to any higher standard at the stage when the patent application must in practice be made. The test is relatively undemanding****. But it cannot be deprived of all meaning or reduced, as Floyd LJ's statement does, to little more than a test of good faith. Indeed, if the threshold were as low as he suggests, it would be unlikely to serve even the limited purpose that he assigns to it of barring speculative or armchair claims."*

[5] *Warner-Lambert Company LLC v Generics (UK) Ltd (t.a. Mylan) & Anor.*, [2018] UKSC 56

24 In the following paragraph of this judgment, it set out seven principles concerning the requirement for plausibility in medical use claims. These principles are discussed and listed in para 4A.29.4 of the IPO's Manual of Patent Practice[6]. I find this list a helpful reminder when considering the plausibility of a claim to a medical use; i.e.

> *i)* *The proposition that a product is effective for the treatment of a given condition must be plausible.*
>
> *ii)* *It is not made plausible by a bare assertion to that effect, and the disclosure of a mere possibility that it will work is no better than a bare assertion.*
>
> *iii)* *The claimed therapeutic effect may be rendered plausible by a specification showing that something is worth trying for a reason; i.e. not just because there is an abstract possibility that it would work but because reasonable scientific grounds are disclosed for expecting that it might well work. The disclosure of those grounds marks the difference between a speculation and a contribution to the art.*
>
> *iv)* *Although the disclosure need not definitively prove the assertion that the product works for the designated purpose, there must be something that would cause the skilled person to think that there was a reasonable prospect that the assertion would prove to be true.*
>
> *v)* *That reasonable prospect must be based on a direct effect on a mechanism specifically involved in the disease, this mechanism being either known from the prior art or demonstrated in the patent per se.*
>
> *vi)* *This effect on the disease process need not necessarily be demonstrated by experimental data. It can also be demonstrated by a priori reasoning.*
>
> *vii)* *This evidence or reasoning must appear in the patent. The disclosure may be supplemented or explained by the common general knowledge of the skilled person. However, it is not enough that the patentee can prove that the product can reasonably be expected to work in the designated use, if the skilled person would not derive this from the teaching of the patent.*

25 The *Warner-Lambert* judgment also makes clear that the specification **as filed** must make the claimed use plausible; data filed after the filing date of the patent can only be used to confirm an effect made plausible in the specification or to refute a contention that the treatment does not actually work; it cannot be a substitute for sufficient disclosure in the specification.

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[6] See IPO Manual of Patent Practice (Manual of Patent Practice - Guidance - GOV.UK (www.gov.uk)). Section 4A, especially paragraphs 4A.29 and 4A29.2 - 4A.29.5.

***Section 14(5) - Support***

26 Section 14(5) relates to the claims and reads as follows (my emphasis added):

> ***The claim or claims shall –***
> *(a) define the matter for which the applicant seeks protection;*
> *(b) be clear and concise;*
> ***(c) be supported by the description;***
> *(d) relate to one invention or to a group of inventions which are so linked as to form a single inventive concept. ….*

In the present case we are concerned specifically with Section 14(5)(c) (as highlighted above).

27 As set down in section 130(7) of the Act, section 14(5) is intended to have, as nearly as practicable, the same effect as the corresponding provision of the EPC, Article 84, and of the PCT, Article 6. Both provisions use essentially the same wording as section14(5)(a)-(c) of the Act.

28 It is established practice in UK law that the form of the claim is a matter for the applicant, and that any claim which fulfils the requirements of the Act is acceptable. The claims as a whole should aim to define and delimit the features of the invention, with the independent claims clearly establishing the essential features of the invention as well as providing enough details of interrelationship, operation or utility to establish that the invention achieves the intended objectives. Section 14(5)(c) requires that the scope of the invention, as defined in the claims, is consistent with what is disclosed in the specification, and not so broad that it goes beyond the invention, yet not so narrow that it deprives the applicant of a just reward for the disclosure of his invention.

*Support for second medical use claims*

29 A claim to the use of a substance or composition in therapy, surgery or diagnosis requires support by evidence of its likely efficacy in that use. This requirement follows from the decision by the Patents Court in *Prendergast*[7]. This case concerned support for Swiss-type second medical use claims and held that, as such claims are distinguished from the prior art by their use, this use must be supported by evidence. The conclusion of the judge, Neuberger J, as he then was, can be summarised as follows:

> (1) The absence of any practical evidence of the idea (i.e., the use of a known pharmaceutical for a new use) working involved the absence of a description.
>
> (2) Whether or not there was an adequate description for the purposes of section 14(5)(c) of the Act had to be judged by reference to the nature of the application. Where there was a claim for the use of a known pharmaceutical in the preparation of a medicament for the treatment of a particular condition, the specification had to provide, by way of description, enough material to enable the

[7] *Prendergast's Applications* [2000] RPC 446

relevantly skilled man to say that this medicament did treat the condition alleged. Mere assertion was insufficient.

(3) It was not practical to lay down what the tests should be in each case but it was clear that, in general, relatively rudimentary tests would suffice. It was not necessary for an applicant to have carried out full rigorous detailed and conclusive tests.

30 The Hearing Officer in IPO decision *Hoffmann-La Roche's Application* (BL O/192/04)[8] applied the same reasoning to claims in the first medical use format because the essential feature of such claims is the intended use and so there must be support for it. The form of evidence is not critical; the application may provide *in vivo* or *in vitro* data, and *in silico* modelling data may be sufficient if it is considered to provide a credible basis for support. Thus, in the case of inventions having at their heart a medical use, the description should not only identify a condition that may be treated but must show by reference to tests that the treatment is a reality and not just a possibility[9]. An applicant does not have to restrict their claims to the specific embodiment described, but the width of the claims must be properly supported by the description of the invention in the specification.

31 In *Prendergast*, the court found that support for the therapeutic use must be found in the specification. As such, later filed evidence cannot overcome the absence of any such support in the application as filed. This decision was acknowledged with approval by the House of Lords in *Conor v Angiotech*[10], and the requirement for some evidence in the application to support second medical use claims was confirmed by the Patents Court decision in *El-Tawil's Application*[11].

***Relationship between Section 14(3) and Section 14(5)***

32 The Court of Appeal in *Genentech*[12] noted that lack of support is not a ground which can be addressed after a patent is granted, unlike the provision concerning sufficiency. The comments of Dillon LJ therein (at page 236, line 50 - page 237, line 3) are a useful guide to the approach to be adopted:

> *"The Patent Office ought to have very clearly in mind that it is undesirable to allow claims the object of which is to cover a wide and unexplored field or where there is no disclosure in the specification which is in any way coterminous with the monopoly indicated in the claims."*

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[8] For full text of Office decision BL O/192/04 see Intellectual Property Office - Patents Decision

[9] See (a) *Hoerrmann's Application* [1996] RPC 341; (b) *Consultant Suppliers Ltd's Application* [1996] RPC 348.

[10] *Conor v Angiotech* [2008] RPC 28

[11] *El-Tawil's Application* [2012] EWHC 185

[12] *Genentech Inc's Patent*, [1989] RPC 147

33 The importance of a correct decision pre-grant on the question of lack of support was further emphasised by Aldous J in *Schering Biotech*[13], and he went on to point out (at page 252, line 53 - page 253, line 2) that the substance of the disclosure, rather than its form, was the key issue:

> *"I do not believe that the mere mention in the specification of features appearing in the claim will necessarily be a sufficient support. The word 'support' means more than that and requires the description to be the base which can fairly entitle the patentee to a monopoly of the width claimed."*

34 It is often the case that the requirements of section 14(5) of the Act overlap with those of section 14(3) as both are concerned with the relationship between the extent of disclosure and the scope of the claims. As pointed out by Lord Walker in *Generics v Lundbeck* (at paragraph 20)[14] :

> *"The disclosure must be such as to enable the invention to be performed…to the full extent of the claims. The question of whether there is sufficient enabling disclosure often interacts with a question of construction as to the extent of the claims".*

35 This is particularly apparent in applications where the claims are speculative, as argued by the examiner in the present case, and therefore objections can be raised under both section 14(3) and section 14(5)(c).

36 At the hearing, Mr Wotherspoon argued that section 14(3) and section 14(5)(c) should be considered together, because the issue is not of sufficiency and support, but of plausibility in the round. He argued that *Prendergast* is incorrect in its assertion (at page 448 line 3-7) that section 14(5)(c) cannot be invoked as a ground of attack post-grant. This is because, from Mr Wotherspoon's understanding of Lord Hoffman's reasoning in *Biogen*[15], section 14(3) and section 14(5)(c) act together to make the claim insufficient.

37 At the hearing, I explained that section 14(5)(c) is a requirement of the claims of the application (in that they need to be supported by the description), whereas section 14(3) is a requirement of the description (in that it needs to provide a disclosure that enables the invention as claimed). Objections may arise during the examination process under section 14(5)(c), that the claims lack support from the description, but where the invention may still be sufficiently enabled, and so no objection under section 14(3) would be warranted. Such objections under s14(5)(c) alone would not be grounds for an attack post-grant.

38 However, and this is where the reasoning of Lord Hoffman in *Biogen* applies, (where he, in turn, is applying reasoning from *Asahi Kasei Kogyo KK's Application*[16]*),* if there

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[13] *Schering Biotech Corp.'s Application* [1993] RPC 249

[14] *Generics v Lundbeck* [2009] RPC 13

[15] *Biogen Inc. v. Medeva plc* [1997] RPC 1

[16] *Asahi Kasei Kogyo KK's Application,* [1991] RPC 485

is no enabling disclosure as required by section 14(3), then it would follow that the description does not support the claims. In *Prendergast*, Neuberger J found that the description did not support the claims because there was no evidence in the application that the proposed uses of the claimed medicament would work. I consider that this conclusion is in no way inconsistent with the reasoning in *Biogen* that the description does not support the claims because there was no enabling disclosure. I therefore disagree with Mr Wotherspoon's opinion that *Prendergast* should be disregarded as relevant case law, and that section 14(3) and section 14(5)(c) should be considered together as 'plausibility' rather than separately.

39 Nevertheless, whilst I will consider each of these sections of the Act separately below, there will inevitably be some overlap even though, for section 14(3), I am starting with what is claimed and, for section 14(5)(c), I am starting with what is in the description as filed.

## Analysis

### *Sufficiency under section 14(3)*

40 As per the principles set out in *Eli Lilly*, the first step is to construe the claims, as they would be understood by the skilled person, interpreting them in light of the description and any drawings in the application as filed, as instructed by section 125(1) of the Act and taking into account the Protocol to Article 69 of the EPC. To do this, I first need to identify the relevant skilled person.

*The person skilled in the art (for sufficiency purposes)*

41 It is worth noting, that for the purposes of section 14(3), the skilled person is trying to make the invention work and does so in light of the common general knowledge at the time the patent was filed. In other words, whilst the skilled person may be an uninventive, but technically competent, person[17] with average skill and intelligence, they will have the patent in front of them and they will be "*trying to carry out the invention and achieve success, … not searching for a solution in ignorance of it" [3].* Furthermore, they are not bound to "*carry out the invention precisely as described and can use the common general knowledge to perform the invention and make any obvious changes that may be necessary, provided of course that any work involved is not undue*"*[18].* The skilled person may also consult someone else on a certain point when trying to implement the teaching of the patent[4].

42 Both the applicant and the examiner agree that the skilled person may comprise a team of people, but there is some disagreement around the composition of that team. The examiner considers that, within the field of diagnosis, treatment and clinical management of pancreatitis, the skilled team would include a physician, a pharmacologist and a pharmacist. Whilst the applicant also agrees that the team would include a clinician familiar with dealing with the symptoms of pancreatitis, and a clinical pharmacologist with experience in pharmacokinetics and skill in

[17] *Mentor Corporation v Hollister Inc.,* [1991] FSR 557

[18] *Regeneron Pharmaceuticals In v Kymab Ltd. & Novo Nordisk,* [2018] EWCA Civ 671

understanding clinical trial data, he is also of the opinion that a molecular biologist and a clinician familiar with treating inflammatory illnesses using canakinumab would also be present.

43 I agree with both parties that the team would include a clinician familiar with dealing with the symptoms and clinical management of pancreatitis. They would also have a knowledge of the pathogenesis of acute pancreatitis (AP), that it is the result of inflammation of the pancreas, and that it can recur. I also agree that a clinical pharmacologist would also be part of the team, and they would be able to study the effects of canakinumab and make recommendations on its use based upon the available research. A pharmacist would also be present to provide advice on dosage regimes.

44 However, I disagree with the applicant that the skilled team would include a clinician familiar with treating IL1-β-mediated inflammatory diseases using canakinumab. In his skeleton arguments, Mr Wotherspoon has provided details of what was known about canakinumab, and the diseases that it has been shown to treat. Whilst this drug has been authorised for the treatment of certain autoinflammatory diseases, these diseases are distinct from pancreatitis, as well as distinct from each other. I do not think that the clinicians treating them would be the same, in the same way that a clinician using methotrexate to treat rheumatoid arthritis would not be the same as a clinician using methotrexate to treat cancer. Nevertheless, the clinician familiar with dealing with the symptoms of AP would be aware of the role of pro-inflammatory cytokines, including IL-1β, in the progression of this disease.

45 I also disagree with the applicant that a molecular biologist would be part of the skilled team trying to make the invention work. As I pointed out above, for the purposes of section 14(3) of the Act, the skilled person / team is trying to carry out the invention to achieve success. As the invention relates to a clinical therapy, I do not consider that a molecular biologist would play a role in enabling the invention.

46 However, when I consider the skilled team for the purposes of inventive step, I will return again to consider the possible involvement of a molecular biologist (see discussion on inventive step below).

*Claim construction*

47 Turning now to the construction of claim 1. The claim is in the format of a second medical use claim, which defines a new second medical use for a known agent. Both the examiner and the applicant agree that the correct interpretation of the term '*for use*' in a second medical use claim is '*suitable and intended for use'*[19]*…'in trying to…*'[20], with the agent in this case being an anti-IL1β antibody.

48 The disease in question is also fairly straightforward and is no cause of dispute. Throughout the prosecution, the applicant has emphasised that chronic and acute pancreatitis are two distinguishable diseases, and, at the hearing, Mr Wotherspoon agreed that by its nature, AP was something that could be treated but can recur. The

[19] *Hospira v Genentech* [2014] EWHC 1094

[20] *Bristol Myers Squibb v Baker Norton Pharmaceuticals* [2001] RPC1

examiner also agrees with this. I also consider the identification of the patient subgroup as someone who has had a prior event of AP to be clear; the patient subgroup is not intended to encompass those who have no history of AP. It is also evident that the intention is to prevent a recurrence in an event of AP, and this would inherently require that the patient had already recovered from at least one earlier bout or prior event of acute pancreatitis (AP).

49 Turning now to consider what is intended by the phrase (my emphasis in underline) '*for reducing the risk of having an event of acute pancreatitis*', I note that the description states that the use is for '*preventing or reducing the risk'*. In his letter dated 26 July 2022, as well as in his skeleton arguments, the applicant has stated that the term '*for reducing the risk*' is intended to encompass prevention of an event of AP. The examiner does not wholly agree with this construction proposed by the applicant. The examiner considers that the skilled person would understand this phrase to mean *'trying to prevent an event of acute pancreatitis'*. The applicant counters that there is no difference in the scope of protection here but does not state whether he agrees with the change to construction proposed by the examiner.

50 Reading the specification through the eyes of the skilled person, I think that '*trying to prevent*' would be seen as synonymous with *'reducing the risk*' (and hence would essentially be redundant), but both would have the underlying intention of preventing a further bout of AP. In light of the wording in the description, I am therefore happy to accept the applicant's construction here that this aspect of the claim should be construed as '*preventing or reducing the risk'* and not '*trying to prevent*' as suggested by the examiner.

51 The examiner points out that the use to 'reduce the risk' of having an event of AP may overlap with the 'treatment' of an attack of AP, but argues that this is distinct from methods of treating AP. The applicant on the other hand, in his letter dated 26 July, considers that the meaning of the claim does not exclude the treatment of an ongoing episode of pancreatitis, and that the skilled person, taking a purposive approach to construction, would reach the same conclusion. Nevertheless, when pressed at the hearing, Mr Wotherspoon agreed with my understanding that the intention is not to treat a single attack, or to take the treatment when you have an attack, rather it is the prolonged use of the IL-1β antibody (or fragment thereof) that prevents AP from recurring.

52 Therefore, I agree with the examiner that the skilled person would understand that the claim does not define the treatment of an ongoing attack of AP, and instead is directed at preventing or reducing the risk of another attack of AP after the patient has already recovered from an earlier attack. That an attack of pancreatitis may inevitably be treated if the patient was already taking an IL-1β antibody as part of a prophylactic regimen would appear to be coincidental to the therapeutic regime, and not an intentional part of it.

53 I therefore construe claim 1 as "*an IL-1β antibody or functional fragment thereof suitable and intended for use in preventing or reducing the risk of a patient experiencing a further attack of acute pancreatitis after the patient has already recovered from an earlier attack of acute pancreatitis*".

*Requirement for sufficiency under section 14(3)*

54 Now that I have construed the claim, I will address whether it meets the requirements of section 14(3). In this case, I must decide whether the IL-1β antibody would be suitable for preventing or reducing the risk of a patient experiencing a further attack of pancreatitis.

55 I will first consider what is disclosed in the specification as filed. The specification sets out the background to AP, the presenting symptoms of this condition, how it is managed and how even when alcohol and gallstones have been eliminated as a cause, around 10% of cases suffer from recurring bouts of AP with no clear underlying cause. There is discussion of how interleukins, including IL-1β, are mediators of the inflammatory response, and how C-reactive protein (hsCRP) is a marker for inflammation. I consider this all to be common general knowledge.

56 With regards to experimental detail, the figures and the section of the specification, as filed, entitled '*Detailed Description of the Disclosure*' are essentially a reproduction of the relevant parts of US 9,683,038 B2 (*Thuren*)[21] (and/or its family members, hereafter referred to as *Thuren*). This prior art document discloses methods of reducing the risk of experiencing a cardiovascular event in a patient that has suffered a cardiovascular event. The figures in *Thuren* show how hsCRP levels reduce following administration of the anti-IL-1β antibody canakinumab in patients with gout or type 2 diabetes mellitus (T2DM), both of which are inflammatory conditions mediated by interleukins, including IL-1β. There is no disclosure of the reduction of hsCRP levels in AP using canakinumab. The description provides details of the levels of hsCRP of the patient with gout or T2DM prior to receiving canakinumab, as well as the dosage regime for the administration of the antibody. However, I note that there is no experimental evidence in the application as filed supporting this dosage in patients with AP or showing the levels of hsCRP in patients with AP. Thus, there is no experimental data provided in the application that has not already been disclosed in the prior art and, more significantly, none of the experimental evidence provided in the application demonstrates that inhibition of IL-1β would be an effective treatment for AP.

57 In his skeleton arguments, the applicant agreed with the examiner that the examples demonstrate how canakinumab *might* be administered in order to achieve the prevention or reduction of an AP event. He also confirmed that no clinical trials have been conducted for this proposed therapy, and any reference to phase II clinical trials is for the treatment of other indications. The examiner referred to a paragraph in Example 1 which states that '*the 50mg and 150mg canakinumab dosing schedule has been selected on the basis of anticipated efficacy, safety, and biomarker modelling data'*, and states that '*everything is guesswork regarding the use of canakinumab for preventing or reducing the risk of an event of AP in a patient who has had a prior event of AP*'. It is therefore evident that the present invention is based upon supposition.

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[21] US 9,683,038 B2, Thuren et al., 20 June 2017, *"Methods of reducing the risk of experiencing a cardiovascular (CV) event or a cerebro-vascular event in a patient that has suffered a qualifying CV event";* the relevant figures reproduced from this US patent in the present application are Figures 2, 3, 4, and 5 (at bottom left); the relevant text reproduced from this patent in the present application is that from col 3, line 11 to col 4 line 54. See also official examination report dated 6 December 2022 from the examiner; especially para 33.

58 That said, mere assertion in itself is not necessarily an indication that the application lacks sufficiency, provided that there are reasons for the skilled person to believe that what is proposed would actually work. In other words, what is proposed in the patent needs to be *plausible*.

59 As noted above, *Warner Lambert* is the leading UK authority around how plausibility applies to the sufficiency of second medical use inventions. Lord Sumption in the Supreme Court agreed with the two lower courts that it was not enough to assert that a known compound was efficacious for treating a specified condition; the patentee must disclose reasons that make this assertion plausible. The concept of plausibility originates from the EPO Boards of Appeal, where over the years a number of decisions have addressed what is deemed to be '*plausible'*, and Lord Sumption took these into account when setting out the threshold for plausibility, and arriving at the seven principles that I have listed above and which were referred to by the examiner during the examination process.

60 It is of no surprise that the applicant and the examiner are at odds with regards to what is required to demonstrate whether the claimed invention is plausible. At the hearing and in his skeleton arguments, Mr Wotherspoon repeatedly pointed out that the examiner had agreed that the treatment of AP with canakinumab was plausible, and that it should therefore follow that the same should be true of using canakinumab to prevent or reduce the risk of having an event of AP.

61 However, as I discussed above when construing the claim, and as I pointed out to Mr Wotherspoon during the hearing, there is a distinction between (a) treating an attack of AP and (b) preventing or reducing the risk of an attack of AP, and so I do not agree that if one of (a) or (b) is plausible, then the other will be too.

62 In terms of what is required in order to demonstrate whether the claimed invention is plausible, I will take guidance from Lord Sumption's seven principles (see above). Essentially, I need to decide whether the application in suit, supplemented by common general knowledge, renders plausible the assertion that an anti-IL-1β antibody (particularly canakinumab) can prevent or reduce the risk of recurrent AP in a patient who has already suffered from a bout of AP (*Warner-Lambert* principles (i) and (vii)).

63 A mere possibility that it will work will not be enough (*Warner-Lambert* principle (ii)), and the specification must show that there is a reason for trying an anti-IL-1β antibody to prevent or reduce the risk of recurring AP, and that there are reasonable scientific grounds that it might work (*Warner-Lambert* principle (iii)). That interleukins are key mediators in the inflammatory response is disclosed in the specification, although this is nothing new and would be well known to the skilled person. It is also known that an anti-IL-1β antibody can be used to inhibit IL-1β in other inflammatory diseases. The specification supposes that antagonism of IL-1β mediated inflammation is an attractive target for ameliorating bile / pancreatic duct vessel wall inflammation associated with non-alcohol associated, non-gallstone associated recurring AP, but there is no corroborating evidence demonstrating this.

64 Whilst the specification does not need to definitively show efficacy, it does need to demonstrate to the skilled person that there was a reasonable prospect that administration of an anti-IL-1β antibody would prevent or reduce the risk of a patient experiencing a further bout of pancreatitis (*Warner-Lambert* principle (iv)). That

reasonable prospect must be based on a direct effect of a mechanism involved in the disease, known either from the prior art or the specification itself (*Warner-Lambert* principle (v)), but it need not necessarily be demonstrated by experimental data; it can also be demonstrated by *a priori* reasoning (*Warner-Lambert* principle (vi)).

65 The only experimental data provided in the specification as filed is data demonstrating a reduction in the inflammatory marker hsCRP when canakinumab is administered to patients suffering from gout or T2DM. Dose response curves indicating how high levels of hsCRP in T2DM patients are reduced over time by the administration of canakinumab are also provided. There is therefore some evidence that demonstrates that an anti-IL-1β antibody can reduce high levels of inflammation. It would therefore follow that administration of an anti-IL-1β antibody *to treat an attack of acute pancreatitis*, after it had started, may be plausible. I note that the examiner also came to this conclusion.

66 However, and I think it is important to emphasise this point, as has already been discussed, the claim is not in my view a claim to the treatment of AP (and indeed Mr Wotherspoon confirmed this at the hearing). Rather the claim is to prevent or reduce the risk of a patient experiencing a further bout of pancreatitis after they have recovered from a previous attack of AP, and the dosage regime in the specification provides continuous prophylactic administration of the anti-IL-1β antibody. This would mean that the antibody is to be administered prior to the onset of any inflammation in the pancreas, and not when there are high levels of inflammation (as indicated by high hsCRP levels) in the early stages of pancreatitis.

67 At the hearing, Mr Wotherspoon went to lengths to explain the role of the inflammasome in the mediation of inflammation, and how this would be part of the skilled person's common general knowledge. It is for this reason that he considered a molecular biologist to be part of the skilled team, although I stand by my reasoning above that, for the purpose of trying to make the invention work, I do not consider that a molecular biologist would be part of the skilled team.

68 Nevertheless, I do believe that a clinician who specialises in dealing with the symptoms and clinical management of pancreatitis would also have some knowledge of the inflammatory response and its role in the onset of pancreatitis. They would appreciate that the aetiology of pancreatitis is complex, and that the inflammatory cascade that occurs during inflammation at the onset of acute pancreatitis will involve a number of pro-inflammatory cytokines, including IL-1β, and that the degree of inflammation correlates with the severity of the attack. But would they go so far as to consider that administering an anti-IL-1β antibody to a patient who has recovered from a bout of AP would reduce the risk of further attacks?

69 Mr Wotherspoon is of the opinion that they would, and during the prosecution has referred to the scientific article by *Xu Bin et al.*[22], (hereafter referred to as *Xu Bin*) as supporting his contention that an IL-1β antagonist would reduce the risk of a subsequent attack of pancreatitis.

[22] *Int J Clin Exp Pathol* (2014) 7 (7) pp 3620-3631, *Xu Bin et al.,* "Interleukin-1b induces autophagy by affecting calcium homeostasis and trypsinogen activation in pancreatic acinar cells".

70 Specifically, in his letter dated 26 July 2022 and replicated in his skeleton arguments, Mr Wotherspoon describes how, based on his understanding of *Xu Bin*, IL-1β activation upregulates cellular calcium, leading to activation of digestive enzymes, including trypsinogen, in the pancreas. As trypsinogen is a known instigator of pancreatitis, the applicant surmises that inhibition of IL-1β will prevent upregulation of calcium ions, thereby stopping trypsinogen activation and subsequent pancreatitis. He concludes that regular dosing of an anti-IL-1β antibody in a patient who has already suffered a bout of AP would reduce the risk of a further attack of pancreatitis because it would reduce the amount of active IL-1β released in the pancreas as part of the inflammatory response.

71 I understand that the applicant has presented a theory around why his invention would work. However, I still need to consider whether the skilled person would deem this plausible in light of their common general knowledge. I agree that it would be common general knowledge that trypsinogen activation is known to play a role in AP. I also agree that the inflammatory response, which would include IL-1β activation, is involved in AP, as is a role for impaired autophagy. However, it is also well known that pancreatitis is a complex inflammatory disease, and its pathogenesis is influenced by many different factors. IL-1β is known to be upregulated at the onset of inflammation in response to various stimuli, but it is only one of a number of pro-inflammatory cytokines activated at that time.

72 The *Xu Bin* paper does indicate that IL-1β induces autophagy, and it also demonstrates that IL-1β stimulation of pancreatic cells *in vitro* leads to increases in calcium ions, and that this can be blocked using the inositol-3-phosphate ($InsP_3$) antagonist 2-aminoethoxydiphenyl borate (2APB). This indicates that in this *in vitro* assay, IL-1β stimulation can activate the $InsP_3$ receptor and release calcium from the endoplasmic reticulum. Further assays show that treatment of the cells with IL-1β and 2APB partially inhibits the trypsinogen activation induced by treatment with IL-1β alone, and that 2APB can attenuate AP *in vivo*, indicating that inhibiting the calcium flux may have a protective effect by blocking autophagy. It is important to note here that the authors of this paper point out that they did not determine whether IL-1β activates the $InsP_3$ receptor directly or indirectly, and therefore did not draw a conclusion on whether inhibiting IL-1β directly would provide the inhibitory effects seen with 2APB.

73 I am in agreement with the applicant's opinion that the skilled person would have a knowledge of the cellular processes surrounding inflammation, and how they relate to the onset of AP. As part of this knowledge, they would be aware that $InsP_3$ receptor signalling is incredibly complex because it can be regulated by a wide range of factors, including agonists, antagonists and modulators, and they would appreciate that whilst inhibition of one such modulator etc. may reduce calcium release via the $InsP_3$ receptor, it is unlikely to be sufficient to prevent disease progression. Indeed, in *Xu Bin*, the authors point out that their results imply that IL-1β increases intracellular calcium levels, resulting in a series of events that include impaired autophagy and trypsinogen activation, and that this might aggravate the progression of pancreatitis. I note also that they do not reach a conclusion that pre-treatment with any antagonist of the calcium signalling system, let alone an antagonist of IL-1β, would prevent the onset of AP. They conclude that autophagy does play an important role in helping

pancreatic acinar cells resist external inflammatory mediators during early pancreatitis, and that this ***might*** provide a new strategy in pancreatitis therapy.

74 I accept that trypsinogen activation, calcium signalling, and autophagy are all factors that contribute to the development of AP and also its severity, and that IL-1β is involved in these steps, either directly or indirectly. I also accept that the skilled person would be aware of this and may see IL-1β inhibition as a target for treating acute pancreatitis, especially as it appears that IL-1β activation happens in the early stages and is indicative of severity. However, I disagree with the applicant that this would indicate that inhibition of IL-1β would *'prevent or reduce the risk'* of having an event of pancreatitis in a patient who has had a prior event of pancreatitis.

75 One of the reasons for this is the involvement of the inflammasome, which Mr Wotherspoon went to great lengths to explain during the hearing. He particularly stressed its importance in the signalling process and the inflammatory response, and how it can be activated due to a variety of stimuli. I agree with him that a specialist involved in inflammatory diseases would know of the role of the inflammasome in the mediation of the inflammatory response, and that this does play a role in the progression of AP. It is also known that the inflammasome can activate caspase-1, which converts pro-inflammatory cytokines, including, but not limited to, IL-1β, into their active forms. However, they would also understand that the activation of the inflammasome is part of the inflammatory process, and so an attack of AP would have already begun and so I fail to see how targeting a molecule downstream of this would be capable of preventing or reducing the risk of a subsequent attack of AP.

76 From the prior art cited by both the applicant and the examiner, and from what I have identified as common general knowledge, I consider that IL-1β is a key component in the inflammatory response in the early stages of pancreatitis and plays a role in the severity of the disease. However, I see no evidence to suggest that continuous administration of an anti-IL-1β antibody would prevent or reduce the risk of having an AP event. Furthermore, where canakinumab has been used to treat patients, this has been where these patients have already elevated levels of IL-1β (see Ilaris | European Medicines Agency (europa.eu)[23]). For the avoidance of doubt, there is no reference to pancreatitis (acute or chronic) in this marketing authorisation and none of the inflammatory conditions that *Illaris* (the medicinal product containing the active ingredient *canakinumab*) is approved to treat include pancreatitis.

77 In my view, this is a further indication that in order for the anti-IL-1β antibody to be effective, persistently increased IL-1β is required. This does not appear to be the case for AP, where IL-1β is induced as part of the inflammatory response. In other words, there is no evidence to suggest that until the onset of an attack of AP, driven by the

[23] The marketing authorisation (MA) for *Ilaris*, a medicinal product for human use, which comprises the active ingredient *canakinumab*, discloses the various inflammatory conditions it can used to treat. These conditions are (i) Still's disease, (ii) Gouty arthritis, (iii) Cryopyrin-associated periodic syndromes (CAPS), (iv) Tumour necrosis factor (TNF) receptor associated periodic syndrome (TRAPS); (v) Hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD) and (vi) Familial Mediterranean Fever (FMF). This MA document was identified and referred to by the applicant in his written skeleton arguments dated 5 January 2023, as part of Discussion Topic C. This MA document is also publicly available from the website of the European Medicines Agency (see link above). *Ilaris* has been approved for use as a medicine since 2009.

inflammatory response and, amongst other things, IL-1β activation, the administration of an anti-IL-1β antibody would have any therapeutic effect.

78 I should also note that whilst WO 2010/138939 (which is incorporated by reference in the present application) suggests the use of an IL-1β antibody for preventing a cardiac event, it does not provide any experimental evidence suggesting that such a use would be effective. Likewise *Thuren,* from which the majority of the information in the present application is derived, also has no experimental evidence demonstrating any preventative effect either.

79 Thus, I do not believe that there is anything in the specification, when taking into account the common general knowledge of the skilled team, that is beyond mere speculation and that provides a reason for suggesting an anti-IL-1β antibody would be effective to prevent or reduce the risk of recurrent AP in a patient who has already suffered from a bout of pancreatitis. Whilst I believe that there may be a reasonable prospect that administration of an anti-IL-1β antibody may treat acute pancreatitis once inflammation mediated by IL-1β has begun and levels of IL-1β are elevated, I do not believe that there is any *a priori* reasoning in the specification that suggests the same for preventing or reducing the risk of an attack before inflammation has begun. Therefore, there is nothing in the specification that enables a plausible prediction to be made that the claimed therapeutic effect would work. For the skilled person to determine whether this invention would work on the balance of evidence presented to me, I consider that there would be an undue burden placed upon them to establish this.

80 I therefore conclude that the claims exceed the disclosed contribution to the art, because the assertion that the administration of an anti-IL-1β antibody to prevent or reduce the risk of a further bout of AP in a patient who has already suffered from a bout of pancreatitis is not plausible. The specification therefore does not meet the requirements of Section 14(3) of the Act.

***Support under Section 14(5)(c)***

81 When considering whether there is support for the claimed invention, I need to ask whether the specification (as filed) provides, by way of description, enough material to say that an anti-IL-1β antibody can prevent or reduce the risk of a further bout of AP in a patient who has already suffered from a bout of pancreatitis.

82 The level of support required for a second medical use claim, as laid down in *Prendergast,* is in the wording of the decision "*rudimentary*". The purpose of this is to avoid a situation where, in the words of Neuberger J (as he then was) "*it would be possible to make valid Swiss-type applications in relation to all sorts of speculative uses for established drugs and other chemicals without a shred of evidence as to whether they would work, let alone as to whether they do work. That seems to me to be potentially embarrassing in terms of overwork for the Patents Office. It appears to me to be potentially stifling so far as research and development are concerned. It appears to me to risk giving an uncovenanted benefit to a substantial or rich organisation which might seek to register a remarkable number of wholly speculative patents which, on Dr Prendergast's argument, would be valid"*

83 I consider that this is similar to the level required to show that the invention is plausible discussed in relation to section 14(3) above. The support that is needed is not at the level of *"full rigorous detailed and conclusive tests"* such as the results of clinical trials.

84 Given that the applicant considers that *Prendergast* should be disregarded, it is not surprising that he has provided nothing in the way of arguments around why the claims are not supported by the description. However, I will take into account his arguments around plausibility, where they are applicable to section 14(5)(c) of the Act.

85 The requirement for support in *Prendergast* is, in my view, straightforward. There should be some indication in the application as filed that the invention would work as claimed. This indication should at the very least be in the form of rudimentary tests supporting the intended use. Pure assertion is not sufficient. There are no tests at all in the present application, and therefore I find that by a straightforward reading of the requirements for support according to the decision of Neuberger J (as he was then) in *Prendergast*, the present application fails.

86 While this reading of *Prendergast* might appear to imply a higher threshold of evidence for the requirements of section 14(5)(c) than for section 14(3), where according to *Warner-Lambert*, *a priori* reasoning may be used to argue that the invention is sufficiently disclosed, I do not consider that this is the case or that it leads me to a different result. If *a priori* reasoning will suffice to support the medical use, the question to consider is whether there is *a priori* reasoning to support the contention that an anti-IL-1β antibody can prevent or reduce the risk of a further bout of AP in a patient who has already suffered from a bout of AP. As I have already concluded in my consideration of sufficiency under section 14(3) above, there is no such reasoning in the present application.

87 Therefore, the claims are not adequately supported by the description and I consider that the present application fails to comply with section 14(5)(c) of the Act.

## Inventive step under Section 1(1)(b) and Section 3

88 I have found above that the application is insufficient and lacks support, and these are sufficient grounds for refusal of this application.

89 The examiner also raised an objection under inventive step in his pre-hearing report dated 6 December 2022. He also referred to the possibility of a 'squeeze' between inventive step and sufficiency. In my analysis below, I take note of this and I am aware that any argument that I make in relation to inventive step may in fact undermine the argument that I have made above in relation to sufficiency. This is because the basis of the information being relied upon by the applicant to deem his application sufficient is obtained from the prior art and the common general knowledge of the skilled team, and I have already decided that the present application lacks sufficiency as the assertions made are not plausible in light of the prior art and common general knowledge. This would appear, at least at first, to suggest that the invention is not obvious.

90 However, while being aware of the above possibility, I do believe that it is necessary for me to go on and consider the inventiveness of this application in the event that I am wrong in my conclusion on lack of sufficiency above.

**The relevant law**

91 Whether or not an invention involves an inventive step is the concern of section 1(1)b and section 3 of the Act.

92 Section 1(1)(b) of the Act reads as follows:

> *1(1). A patent may be granted only for an invention in respect of which the following conditions are satisfied, that is to say:*
>
> *(a)…;*
> *(b) It involves an inventive step;*
> *(c)…;*
> *(d)….*

93 Section 3 of the Act, entitled 'Inventive Step' reads:

> *An invention shall be taken to involve an inventive step if it is not obvious to a person skilled in the art, having regard to any matter which forms part of the state of the art by virtue only of Section 2(2) above (and disregarding Section 2(3) above).*

94 Section 2(2) of the Act, which refers to the state of the art, reads:

> *The state of the art in the case of an invention shall be taken to comprise all matter (whether a product, a process, information about either, or anything else) which has at any time before the priority date of that invention been made available to the public (whether in the United Kingdom or elsewhere) by written or oral description, by use or in any other way.*

95 The approach to assessing inventive step is the structured approach found in *Windsurfing International Inc. v Tabur Marine (Great Britain) Ltd*[24] ("*Windsurfing*") as modified by Jacobs LJ in *Pozzoli SPA v BDMA SA*[25] ("*Pozzoli*"). This approach, referred to as the "Windsurfing/Pozzoli" test involves the following steps:

> *(1)(a) Identify the notional "person skilled in the art"*
> *(1)(b) Identify the relevant common general knowledge of that person;*
>
> *(2) Identify the inventive concept of the claim in question or if that cannot readily be done, construe it;*

[24] *Windsurfing International Inc. v Tabur Marine (Great Britain) Ltd.,* [1985] RPC 59

[25] *Pozzoli SPA v BDMA SA* [2007] EWCA Civ 588

*(3) Identify what, if any, differences exist between the matter cited as forming part of the "state of the art" and the inventive concept of the claim or the claim as construed;*

*(4) Viewed without any knowledge of the alleged invention as claimed, do those differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention?*

There was no disagreement between the examiner and applicant regarding the correct approach for the assessment of inventive step.

**Analysis**

*Sufficiency v Inventive Step*

96 Before I begin my analysis of inventive step, it is appropriate for me to refer to the 'squeeze' between sufficiency and inventive step. This possibility was briefly referred to by the examiner in their examination report dated 10 June 2022. The 'squeeze' argument is where the basis for the patent being deemed sufficient relies on the common general knowledge and/or the prior art because it is not disclosed in the specification itself. The argument is therefore that the patent is either insufficient because it is outside the knowledge or ability of the skilled person, or it is obvious because the skilled person would arrive at the invention based upon their common general knowledge.

97 Both sides of the 'squeeze' argument have been considered by the courts. In *Accord Healthcare*[26], Birss J (as he then was) commented (albeit *obiter*) that it was possible that, in certain circumstances, an argument can be made that a claim is inventive but then the claims would lack sufficiency because the patent does not make the invention plausible. In this particular case, there was no experimental data provided nor any reasoning that would give the skilled person basis to establish a credible view that the dosage regime proposed for the drug in question (methotrexate) would have the side effect problem:

*"This case illustrates why in a proper case there can be a squeeze between plausibility for insufficiency and obviousness. ... If it was not obvious to administer a 25 mg dose using a 50 mg/ml concentration in a 0.5 ml volume subcutaneously because of a concern about the risk of side effects, then the patent does not give such a skilled person any comfort at all about that risk. If that skilled person would not administer the formulation to treat RA due to the risk, they would still not do it after reading the patent, and the claim to the use of that formulation would be insufficient."*

98 However, in *Actavis*[27], Carr J pointed out that the '*obvious to try*' criteria is not enough to demonstrate a lack of inventive step, and there must be a fair expectation of success that the route taken would work. He opined that refusing patent protection based upon '*obvious to try*' alone would hinder research and development, which was not the

[26] *Accord Healthcare Ltd v Medac Gesellschaft Für Klinische Spezialpräparate Mbh* [2016] R.P.C. 17

[27] *Actavis Group PTC EHF & Anor v Eli Lilly and Company* [2015] EWHC 3294 (Pat)

intention of the patent system. Conversely, he noted that the requirement for plausibility was to prevent speculative patents, where there was no reason to assume that what was asserted is true.

> *"… the policy considerations underlying plausibility for sufficiency are different from those underlying fair expectation of success for obviousness, which indicates that the standard for assessment of plausibility is not the same as assessment of obviousness. For obviousness, a fair expectation of success is required because, in an empirical art, many routes may be obvious to try, without any real idea of whether they will work. The denial of patent protection based upon the "obvious to try" criterion alone would provide insufficient incentive for research and development in, for example, pharmaceuticals and biotechnology, and would lead to the conclusion that a research program of uncertain outcome would deprive a patent of inventive step. The reason why the court requires that the invention of a patent should be plausible is different. It is to exclude speculative patents, based on mere assertion, where there is no real reason to suppose that the assertion is true*".

99 At the hearing Mr Wotherspoon emphasised the importance of '*obvious to try with a reasonable expectation of success*' when assessing the inventive step of the present invention, and I do not dispute that this is the correct approach.

100 I am mindful of the possibility of a 'squeeze' argument given my finding that the application lacks sufficiency as it is merely speculative in light of the information provided therein and from what the skilled person would understand from the common general knowledge. However, I will keep in mind the cautionary words of Carr J in *Actavis* highlighted above as I begin my analysis of inventive step below.

*Assessment of Inventive Step*

101 Turning now to the structured approach under *Windsurfing/Pozzoli* for assessing inventive step:

*Step (1): (a) Identify the notional "person skilled in the art".*

102 Whilst I have already identified the skilled person above when considering sufficiency, I must now consider afresh who is the skilled person for the purposes of inventive step. This is because the skilled person for the purposes of obviousness is looking at the invention from a different place to the skilled person looking at the invention for the purposes of sufficiency. As set out in *Schlumberger*[28] (at para [64], and in reference to the corresponding Articles of the EPC]):

> "*This is not because a different construction is being given to the phrase 'person skilled in the art' in the different Articles. It is because the phase is being applied to different situations. Where the issue is claim construction or sufficiency one is considering a post-patent situation where the person skilled in the art has the patent in hand to tell him how to perform the invention and what the monopoly claimed is. But* ex-hypothesi *the person*

[28] *Schlumberger Holdings Ltd and Electromagnetic Geoservices AS* [2010] RPC 33

*skilled in the art does not have the patent when considering obviousness and 'the art' may be different if the invention of the patent itself is art changing".*

103 I note that neither the applicant nor the examiner have considered the differences between the skilled person for the purposes of sufficiency and for the purposes of inventive step. I will therefore assume that their arguments in relation to who would be the person (or persons making up the team) skilled in the art are to be applied generally.

104 As with sufficiency, I consider that, for the purposes of inventive step, the skilled person would, in fact, be made up of a team, and that team would include a clinician familiar with dealing with the symptoms and the treatment of pancreatitis. It would also include a clinical pharmacologist who would have an interest in therapeutics for inflammatory diseases, including pancreatitis.

105 In his submissions, the applicant proposed that a molecular biologist would be part of the skilled team, and whilst I disagreed that they would be part of the team trying to make the invention work, I think that this is worth some further consideration for the purposes of inventive step. The applicant considers that such a person, with expertise in the field of inflammation and inflammatory signalling at the cellular level, would be a suitable member of the skilled team. I am inclined to agree with this; in my opinion the skilled person(s), for the purposes of inventive step, would be trying to solve the problem of treating or preventing AP and so this team would include a member who was familiar with how the inflammatory response worked and how it was applicable to pancreatitis.

106 Therefore, for the purposes of inventive step, I agree with the applicant that a specialist in the cellular inflammatory response would form part of the team. Furthermore, for the purposes of inventive step, I disagree with the examiner that the team would include a pharmacist. In my view there would be no need to determine appropriate dosages when trying to solve the initial problem of treating or preventing AP.

*Step (1): (b) Identify the relevant common general knowledge of that person.*

107 The clinician familiar with pancreatitis would have knowledge of the treatment of both acute and chronic pancreatitis. They would also be aware that once gallstones and alcohol had been eliminated as causative factors, the cause of acute pancreatitis (AP) may not be identifiable. They would however know that inflammation played a role, and their knowledge would be supplemented by that of the specialist in the cellular inflammatory response, who would be aware of the role of pro-inflammatory cytokines, including IL-1$\beta$. This specialist in cellular inflammatory responses would understand that mature, active IL-1$\beta$ is produced by cleavage of the pro-IL-1$\beta$ precursor by the enzyme caspase-1, and that the active form binds to the IL-1 receptor. They would also know that IL-1Ra (IL-1 receptor antagonist) is a natural antagonist to IL-1$\beta$ as it competes for binding at the IL-1 receptor. The clinical pharmacologist would have a knowledge of the different therapeutics available for inflammatory diseases, including anti-inflammatories, antagonists for inflammatory mediators, and amongst these would be antibody therapeutics targeting inflammatory cytokines such as IL-1$\beta$.

108 It would also be common general knowledge to the skilled team that inflammation may be detected by elevated plasma CRP levels, and that this is a common marker for the onset of AP.

*Step (2): Identify the inventive concept of the claim in question or if that cannot readily be done, construe it.*

109 I have already construed the claim when dealing with sufficiency above, and this construction still applies. The claim therefore relates to '*an IL-1$\beta$ antibody or functional fragment thereof suitable and intended for use in trying to reduce the risk of a patient experiencing a further attack of acute pancreatitis after the patient has already recovered from an earlier attack of acute pancreatitis*'.

*Step (3): Identify what, if any, differences exist between the matter cited as forming part of the "state of the art" and the inventive concept of the claim or the claim as construed.*

110 In his pre-hearing report, the examiner has cited four documents that he considered to render the invention, as defined in claims 1-16 of the present application, obvious. The applicant however has not addressed any of these documents, and instead has once again referred to *Xu Bin* as the closest prior art.

111 I do not consider that the *Xu Bin* document would be seen as the closest prior art by the skilled team; whilst it suggests a role for IL-1$\beta$ in inducing impaired autophagy and trypsinogen activation in AP, the focus of this document is on the mechanisms behind this (specifically the release of calcium ions into the cytosol in response to IL-1$\beta$ stimulation), and not on providing a therapy for pancreatitis. I consider that, although there is a vague suggestion that these findings may be used to provide a new strategy in pancreatitis therapy, there is no direction as to what part of the findings from the work described in *Xu Bin* may be of use for this purpose. Therefore, I disagree with the applicant that this is the closest prior art for the purposes of inventive step and, as such, I will not consider it further.

112 I note that the first of the four citations identified by the examiner, *Thuren,* was cited for the first time in the pre-hearing report dated 6 December 2022. It is unusual for a new document to be cited so late in proceedings, and in ordinary circumstances, the applicant would be given the opportunity to comment on the relevance of a document before the application progressed to a hearing. However, in the present case, it is clear that *Thuren* forms the basis of the present application, given, as already noted above, that some of the figures and sections of the description from *Thuren* are identical to corresponding parts of the application as filed (see official examination report dated 6 December 2022, especially para 33). As such, the applicant was clearly aware of *Thuren* before the patent was filed. Thus, I am satisfied that *Thuren* can be included as part of the examiner's arguments to demonstrate lack of inventive step.

113 *Thuren* discloses the use of canakinumab for preventing or reducing the risk of a recurrent cardiovascular event or cerebrovascular event in a patient who has already suffered from a qualifying cardiovascular event. It discusses how administration of canakinumab has reduced hsCRP levels in patients with the inflammatory diseases cryopyrin-associated periodic syndrome (CAPS), rheumatoid arthritis, and type 2 diabetes mellitus (T2DM). It also proposes that a direct anti-inflammatory agent, such

as canakinumab, may be effective in a population with an increased risk of cardiovascular disease but who are clinically stable having survived a myocardial infarction event, particularly where there is biochemical evidence of a persistent heightened inflammatory response.

114 Similar to the present application, *Thuren* does not provide any experimental evidence supporting the assertion therein, but it does provide experimental data for the reduction of plasma hsCRP levels using canakinumab. It discloses suggested dosage and administration regimes (which are replicated in the present application). However, enablement is not a requirement when considering a document for the purposes of inventive step, all that is needed is something in the teaching that would direct the skilled person to apply it to the problem at hand. *Thuren* teaches, in general, that an antibody that binds IL-1β, and, in particular, canakinumab, has anti-inflammatory activity which can reduce persistent inflammation.

115 The difference between *Thuren* and the present application is that, whilst both intend to prevent or reduce the risk of IL-1β-mediated diseases, *Thuren* is directed towards cardiovascular events, whereas the present invention is directed towards AP. I therefore need to consider whether the skilled person would find it obvious to use canakinumab to prevent or reduce the risk of other IL-1β-mediated diseases, such as AP.

*Step (4): Viewed without any knowledge of the alleged invention as claimed, do those differences constitute steps which would have been obvious to the person skilled in the art or do they require any degree of invention?*

116 As I have discussed above, the skilled team would include a clinical pharmacologist with an interest in treating inflammatory diseases, and upon reading *Thuren*, I am satisfied that they would consider investigating other possible IL-1β-mediated diseases that may benefit from the administration of canakinumab. While they would know from their common general knowledge that both chronic and acute pancreatitis were such diseases, would they consider pancreatitis as a potential target for the use of canakinumab? More importantly, would they find it obvious to try the administration of canakinumab to prevent or reduce the risk of a further attack of pancreatitis in a patient who has already suffered an attack of AP, and would they do so with any expectation of success?

117 In his pre-hearing report dated 6 December 2022, the examiner refers to three further documents that he considers points towards the use of blockers of IL-1β signalling to reduce the severity of experimental pancreatitis. A publication by Xu Chunfang et al., (hereafter *Xu Chunfang*)[29] and the publication by Shen et al. *(Shen)*[30] both disclose how recombinant human IL-1Ra, an antagonist to IL-1β, can provide protection against chronic pancreatitis and suggest that it may provide an effective treatment against

[29] *Biochemical Pharmacology* (2015) Vol 93, pp 449-460, *Xu Chunfang et al. "*'Recombinant interleukin-1 receptor antagonist attenuates the severity of chronic pancreatitis induced by TNBS in rats"

[30] *Biomedicine & Pharmacotherapy* (2012) Vol 66, pp 83-88, *Shen et al*. "'Recombinant interleukin-1 receptor antagonist attenuates the severity of chronic pancreatitis induced by TNBS in rats

chronic pancreatitis. The publication by Zhang et al. *(Zhang)*[31] discloses how IL-1β levels are significantly increased in severe acute pancreatitis, and how the inhibition of caspase-1, which cleaves IL-1β precursor to the mature IL-1β, decreases IL-1β levels, suggesting a role in alleviating IL-1β mediated organ damage in AP.

118 *Xu Chunfang* and *Shen* therefore demonstrate how the IL-1β antagonist IL-1Ra is a possible therapeutic for chronic pancreatitis, whereas *Zhang* indicates that the reduction in IL-1β levels through inhibition of caspase-1 can alleviate organ damage induced in severe acute pancreatitis. The examiner considers that, whilst these documents do not suggest targeting IL-1β with a view to prevent disease recurrence, the skilled team is taught of the involvement of IL-1β-mediated inflammation in the aetiology of pancreatitis. In light of this, he concludes that it would be obvious for the skilled team, based on the disclosure in any of these three documents, to try to use canakinumab, as per *Thuren*, to reduce IL-1β-mediated inflammation as a means to prevent the recurrence of AP.

119 I find I am in agreement with the examiner that the skilled team (for the purposes of inventive step) would find it obvious to apply the teachings of *Thuren*[32] to an alternative disease mediated by IL-1β in light of *Zhang, Shen* or *Xu Chunfang*. As the skilled team includes a biologist familiar with the inflammatory response and how it applies to pancreatitis, they would consider pancreatitis as one of those diseases, and therefore it would be obvious to try and prevent or reduce the risk of a subsequent attack of AP using canakinumab.

120 But would there be a reasonable expectation of success? The skilled team with a knowledge of the involvement of IL-1β in the onset of AP would, in my view, consider it a logical (i.e. obvious) step to apply the teachings of *Thuren* in light of *Zhang, Shen* or *Xu Chunfang* to AP and that this would have a reasonable expectation of success. This expectation of success would be based upon the disclosure in *Thuren* of reducing the risk of a further cardiovascular event, and the suggestion therein that it could be applied to additional diseases where hsCRP levels were an indicator of inflammation. As noted above, it is part of the common general knowledge of the skilled team that AP was a disease with elevated hsCRP levels.

121 At the hearing, Mr Wotherspoon endeavoured to address the tension between plausibility and obviousness, particularly with the reasonable expectation of success. He argued that the prior art can make the claim plausible but it does not make it obvious. Specifically, by making it plausible, the prior art will make the invention obvious to try, but until you have clinical trials there is no reasonable expectation of success.

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[31] *World Journal of Gastroenterology* (2014) Vol 20, pp 10457-10463, *Zhang et al.,* "Caspase-1 inhibition alleviates acute renal injury in rats with severe acute pancreatitis"

[32] This is where my finding on the role of the prior art *Thuren* for the purposes of inventive step is in contrast to my finding on sufficiency and why I have referred to the so-called squeeze between Inventive step and sufficiency. As explained above, I consider that the present application lacks sufficiency but, in coming to that view, I consider that *Thuren* suggests that administration of an anti-IL-1β antibody to treat an attack of acute pancreatitis, after it had started, may be plausible. This contrasts to the view of Thuren as explained above for the purposes of inventive step

122 Mr Wotherspoon tried to distinguish the present situation from the findings of the Court of Appeal in *Hospira v Genentech*[33], and the Supreme Court in *Actavis v Icos*[34], both of which deal with the obviousness of dosage regime patents, and neither of which provided data from clinical trials. In his arguments, Mr Wotherspoon considered that such dosage regimes are clearly obvious because carrying out investigations into dosage response is routine and, given that the drugs were already known for treating the specific diseases in question, no clinical trials would be needed for such routine procedures. On the other hand, in the present case, which is a *bona fide* second medical use, it would not be known whether it would work until there has been clinical trials because the anti-IL-1β antibody had not been previously used to treat AP.

123 It is clear that Mr Wotherspoon considers that clinical trials are necessary in the prior art in order to render a patent for a new medical use obvious to try with a reasonable expectation of success. I do not dispute that in certain circumstances, clinical trials may be useful in demonstrating the inventiveness or lack thereof, of a patent, but this is entirely dependent upon the facts of the case. In the words of Kitchin LJ (at para 55) in *Novartis AG v Generics*[35]:

> *"What is a reasonable or fair expectation of success will again depend upon all the circumstances and will vary from case to case. Sometimes, as in Saint Gobain, it may be appropriate to consider whether it is more or less self-evident that what is being tested ought to work. So, as this court explained in that case, simply including something in a research project in the hope that something might turn up is unlikely to be enough. But I reject the submission that the court can only make a finding of obviousness where it is manifest that the test ought to work. That would be to impose a straitjacket on the assessment of obviousness which is not warranted by the statutory test and would, for example, preclude a finding of obviousness in the case where the results of an entirely routine test are unpredictable."*

Thus what is important is how routine it would be for the skilled person to perform the experiments that would arrive at the patent, and whether they would do so with any expectation of success.

124 In the present case, it is clear that the applicant is relying upon routine experimentation in order for the skilled person to work the invention, and that this routine experimentation is based upon their understanding that the therapeutic regimen disclosed in *Thuren* could be applied to other auto-inflammatory disorders, such as AP. *Thuren* provides dosage forms and regimes for preventing or reducing the risk of an IL-1β-induced cardiovascular event in a patient who has already had a cardiovascular event, and I consider that conducting clinical trials on patients with similar IL-1β-induced inflammatory conditions, including AP, would be no more than routine.

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[33] *Hospira UK Ltd. v Genentech, Inc*. [2016] EWCA Civ 1185

[34] *Actavis Group PTC EHF and others v Icos Corporation and another* [2019] UKSC 15

[35] *Novartis AG v Generics (UK) Ltd. (trading as Mylan)* [2012] EWCA Civ 1623

125 In my view, if such experimentation was not deemed to be routine, then the skilled person, reading *Thuren* combined with the disclosure from *Xu Chunfang, Shen* or *Zhang,* would not consider applying the teachings therein to AP and would still not consider doing so after reading the present application. This would render the application insufficient for lack of plausibility, demonstrating that in the present case there is a squeeze between plausibility for insufficiency and obviousness.

126 If I am not correct in this assessment and the invention is not obvious, then, as already discussed above, it lacks sufficiency because the skilled person would not deem it to be plausible.

## Conclusion

127 Taking all of the above into account, I find that the present patent application GB1812182.2, in the name of Hugh Robert Wotherspoon, lacks sufficiency and does not comply with section 14(3) of the Act,

128 I also find that the invention, as claimed in claims 1-16 of this application, lacks support and does not comply with section 14(5)(c) of the Act.

129 Furthermore, and in the event that I am not correct in my assessment of sufficiency or support, I find claims 1-16 of the application lack an inventive step in light of *Thuren*[21] when read in combination with any one of *Xu Chunfang*[29], *Shen*[30], and *Zhang*[31]. As a result, this application does not comply with section 1(1)(b) of the Act.

130 As this application fails to meet the requirements of the Act under section 14 or under section 1, I refuse this application under section 18(3) of the Act.

## Appeal

131 Any appeal must be lodged within 28 days after the date of this decision.

**Dr L Cullen**
Deputy Director, acting for the Comptroller