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Case No: HP-2015-000053 HP-2016-000016

IN THE HIGH COURT OF JUSTICE
CHANCERY DIVISION
PATENTS COURT

Royal Courts of Justice
Rolls Building
Fetter lane, London
EC4A 1NL

Date: Friday 3rd March 2017

Before :

THE HON. MR JUSTICE HENRY CARR

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Between :

FUJIFILM KYOWA KIRIN BIOLOGICS COMPANY LIMTED **(a company incorporated under the laws of Japan)**	**Claimant in HP-2015-000053**
(1) SAMSUNG BIOEPSIS UK LIMITED **(2) BIOGEN IDEC LIMTED**	**Claimants in HP-2016-000016**
- and –	
ABBVIE BIOTECHNOLOGY LIMITED **(a company incorporated under the laws of Bermuda)**	**Defendant in HP-2015-000053 And HP-2016-000016**

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MR ANDREW WAUGH QC and DR JUSTIN TURNER QC (jointly instructed by Gowling WLG(UK) LLP (solicitors for Fujifilm Kyowa Kirin Biologics Co., Ltd.), Powell Gilbert LLP (solicitors for Biogen Idec Limited) and Simmons & Simmons LLP (Solicitors for Samsung Bioepis UK Limited)) MR GEOFFREY PRITCHARD (instructed by Gowling WLG (UK) LLP (UK)) and MISS KATHERINE MOGGRIDGE (jointly instructed by Powell Gilbert LLP and Simmons & Simmons LLP) appeared for the Claimants.

MR MICHAEL TAPPIN QC, MR ANDREW LYKIARDOPOULOS QC , MR MARK CHACKSFIELD and MR JEREMY HEALD (instructed by **Herbert Smith Freehills LLP**) for the **Defendant .**

Hearing dates: 16, 17, 18, 19, 20, 23, 24, 26, 27 January and 1, 2, 3 February 2017

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Judgment Approved

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Annex 1: Agreed chronology of events in relation to entitlement to priority

Mr Justice Henry Carr:

Introduction

1. The Defendant ("AbbVie") is the proprietor of a number of patents relating to the antibody adalimumab, sold under the trade mark Humira. Humira is the highest selling prescription drug in the world by global sales, achieving net sales in 2014 in excess of US$12.5 billion. Adalimumab is a fully human antibody that binds and neutralises the activity of TNFα. The basic patent for adalimumab (EP 0,929,578) and its associated UK Supplementary Protection Certificate ("SPC") (GB/04/002) will expire on 15 October 2018.

2. Humira has been approved for the treatment in adults of, among other indications, rheumatoid arthritis ("RA"), psoriatic arthritis and psoriasis. The basic dosage regimens for those indications, as set out in the Summary of Product Characteristics, specify or include the administration of 40 mg adalimumab every other week as a single dose via subcutaneous injection ("40mg sc eow"), and, in some cases, weekly. AbbVie has obtained or applied for a number of patents and divisionals for adalimumab which claim the use of this dosage regimen in the treatment of various indications.

3. The Claimants in these proceedings (respectively "FKB" and "SB/Biogen") each intend to market a biosimilar adalimumab product in Europe, including in the United Kingdom, after expiry of the basic adalimumab patent and its associated SPCs, if they can clear the way of secondary patents before then. Due to regulatory requirements it is necessary for the Claimants to utilise the dosing regimens authorised for Humira. The Claimants seek declarations that their products were obvious and/or anticipated at the claimed priority dates of certain of AbbVie's patents, namely 8 June 2001 and 18 July 2003. The declarations sought by FKB and SB/Biogen are in the following terms:

> "A Declaration pursuant to CPR 40.20 and/or the inherent jurisdiction of the Court that importing into the United Kingdom and offering to sell and dispose of, and to sell and dispose of, and to keep for such sale or disposal in the United Kingdom, the Claimant's products containing their biosimilar monoclonal antibody to the antibody adalimumab (Humira) for the treatment of rheumatoid arthritis, psoriatic arthritis and/or psoriasis by the administration of 40mg every other week by subcutaneous injection for:
>
> (a) rheumatoid arthritis would, in so far as the dosing regimen is concerned, have been obvious and/or anticipated at the date from which EP (UK) 1 406 656 was entitled to claim priority, whether or not co-administered with methotrexate (as would administration of 40 mg by subcutaneous injection every week in the case of monotherapy in rheumatoid arthritis); and

> (b) psoriasis and/or psoriatic arthritis would, in so far as the dosing regimen is concerned, have been obvious and/or anticipated at 18 July 2003 (as would administration of 40 mg by subcutaneous injection every week) (whether as an initial or continuing dosing regimen)."

4. These proceedings started as revocation actions, in which so called "*Arrow*" declarations were also sought. The patents in suit, at various times, were EP (UK) 1,406,656 ("the 656 patent") in respect of autoimmune disorders including RA, and EP UK 1,944,322 ("the 322 patent") in respect of psoriasis and psoriatic arthritis. The Claimants indicated that they intended to add EP UK 2,940,044 ("the 044 patent") in respect of RA to the proceedings, once it was granted. However, since commencement of proceedings AbbVie has disapproved of the text of the 656 and 322 patents, with the effect of revoking them centrally, and so abandoning them for all designations, and de-designated the 044 patent, for the UK only. AbbVie has also given undertakings, the effect of which, it claims, gives at least as much protection to the Claimants as the relief sought in the declarations. It also offered to pay the costs of the proceedings if its proposal was accepted and provided draft consent orders.

5. This was not acceptable to the Claimants, who invited AbbVie to submit to judgment, which would end the proceedings and result in the grant of the declarations. AbbVie refused to do this. AbbVie has made a series of applications to strike out or obtain summary judgment, which have not been successful. AbbVie continues to resist the grant of any declarations, which has resulted in a major three week trial.

The principal issues

The priority case

6. The claimed priority date for the 656 patent was 8 June 2001. If priority was not validly claimed, then by a letter dated 9 January 2017, AbbVie has admitted, for the purposes of these proceedings only, that the treatment of RA by the administration by subcutaneous injection of 40mg every other week of adalimumab (whether or not co-administered with methotrexate) is anticipated by an abstract entitled "*The Armada trial: A double-blind placebo controlled trial of the fully human anti-TNF monoclonal antibody adalimumab (D2E7) in patients with active RA on methotrexate (MTX)*" by E. Keystone et al., in Arthritis & Rheumatism (Arthritis Rheum., 44(59), S213, abstract 965) published in November 2001 ("Keystone 2001").

7. The Claimants challenge the entitlement to claim priority from US Patent Application No. 60/296,961 ("US 961"). The Claimants allege that the applicant for the 656 patent, Abbott Laboratories (Bermuda) Ltd ("Abbott Bermuda") was not entitled to claim priority from US 961 because it was not the successor in title to the applicants for US 961, who were the inventors, Dr Fischkoff, Dr Weiss and Dr Kempeni. The priority attack is not based upon an absence of disclosure in US 961. Rather, the Claimants challenge the chain of title by which Abbott Bermuda claims to be entitled to claim priority under Article 4A of the Paris Convention. This has resulted in a complex investigation, which has included issues of US and German law, as well as extensive evidence of fact, much of which has been the subject of cross-examination.

The technical case

The administration of the Claimants' proposed products at a dose 40mg sc every other week for the treatment of RA

8. This is the only substantial technical aspect which is still in dispute. The Claimants allege (and AbbVie denies) that the administration of the Claimants' proposed products at a dose of 40mg sc eow (whether as a monotherapy or with methotrexate) for the treatment of RA lacked inventive step as of 8 June 2001 over certain prior art publications by Dr Kempeni, when read in the light of common general knowledge. The prior art refers to adalimumab as "D2E7", which is a designation that I shall adopt when considering the issues. The prior art relied on is:

    i) A paper entitled: *"Preliminary results of early clinical trials with the fully human anti-TNFα monoclonal antibody D2E7"* by Joachim Kempeni published in Annals of Rheumatic Diseases (*Ann. Rheum. Dis.*, 1999, 58 (Suppl 1), I70-I72) ("Kempeni 1999"); and

    ii) A paper entitled *"Update on D2E7: a fully human anti-tumour necrosis factor α monoclonal antibody"* by Joachim Kempeni published in Annals of Rheumatic Diseases (*Ann. Rheum. Dis.*, 2000, 59 (Suppl I), i44-i45) ("Kempeni 2000").

9. It is common ground that Kempeni 1999 would be read in conjunction with the following abstracts, which are expressly referred to in Kempeni 1999, and that Kempeni 2000, which cites Kempeni 1999, would be read in conjunction with Kempeni 1999 and with the abstracts:

    i) An abstract entitled *"A single dose placebo-controlled phase I study of the fully human anti-TNF antibody D2E7 in patients with rheumatoid arthritis"* by L van de Putte et al., published in Arthritis & Rheumatism (*Arthritis Rheum.*, 1998, 41(9), S57, abstract 148) ("van de Putte 1998"),

    ii) An abstract entitled *"Long term efficacy and tolerability of multiple iv doses of the fully human anti-TNF antibody D2E7 in patients with rheumatoid arthritis"* by R Rau et al., published in Arthritis & Rheumatism (*Arthritis Rheum.*, 1998, 41(9), S55, abstract 137) ("Rau 1998"); and

    iii) An abstract entitled *"Efficacy and tolerability of weekly subcutaneous injections of the fully human anti-TNF antibody D2E7 in patients with rheumatoid arthritis"* by M. Schattenkirchner et al., published in Arthritis & Rheumatism (*Arthritis Rheum.*, 1998, 41(9), S57, abstract 149) ("Schattenkirchner 1998").

10. At the close of the trial the Claimants indicated that I could consider Kempeni 1999 and Kempeni 2000 together, as part of a single obviousness attack. However, I will still need to determine obviousness in the light of Kempeni 1999, as crucial parts of the case in respect of Kempeni 1999 are relied on by the Claimants for their case on Kempeni 2000.

The administration of the Claimants' proposed products at a dose 40mg sc every week for the treatment of RA

11. By a letter dated 9 January 2017, AbbVie admitted, for the purposes of these proceedings only, that the treatment of RA by the administration of adalimumab at a dose of 40mg sc every week for the treatment of RA was anticipated or obvious as of 8 June 2001. This was inevitable in the light of Kempeni 2000, which expressly discloses this dosage regimen for adalimumab.

The administration of the Claimants' proposed products at a dose 40mg sc every other week for the treatment of psoriasis and psoriatic arthritis

12. By a letter dated 22 December 2016 AbbVie admitted, for the purposes of these proceedings only, that the treatment of psoriasis and psoriatic arthritis by the administration of adalimumab by subcutaneous injection of 40mg as monotherapy was anticipated/obvious as of 29 January 2004 (the date of publication of the 322 patent). However, it refuses to admit anticipation or obviousness as of 18 July 2003, which was the priority date of the 322 patent and the date specified in the Claimants' declarations. Therefore, the date from which this dosage regimen was anticipated or obvious remains in issue between the parties, although AbbVie did not seek to challenge the Claimants' evidence on this subject in cross-examination.

The declaration case

13. AbbVie submits that the declarations would not serve a useful purpose. It claims that it has taken steps leading to revocation of all patents which are or might have been in issue in these proceedings, and has also given clear and unambiguous undertakings to the Court which are just as useful as the relief sought by the Claimants in the declarations. It argues that since there will never be any UK patent claims to the dosage regimens in question, it would be wrong in principle, and would not serve a useful purpose, to make the declarations.

14. FKB and SB/Biogen's position is that AbbVie is not prepared to offer the relief sought, or even an acknowledgement in terms of the declarations, because it would be an unambiguous indication that the biosimilar products have been cleared in the United Kingdom. The Claimants argue that AbbVie has threatened to pursue proceedings for infringement throughout the world. They suggest that AbbVie refuses to submit to the declarations precisely because they will serve a useful purpose, by removing any confusion in the marketplace, promoting settlement, preventing interference with the Claimants' supply chains between Europe and the United Kingdom and by influencing other courts throughout Europe.

15. Furthermore, the Claimants submit that the latest moves by AbbVie cannot be viewed in isolation. They are part of a course of conduct, whereby AbbVie has dragged out proceedings for as long as possible whilst threatening to sue for infringement, and then has abandoned its patent rights at the last moment, whilst filing further divisionals with very similar claims. According to the Claimants, this strategy is designed to encourage market uncertainty, whilst shielding AbbVie's patents from the risk of a finding of invalidity.

The priority case

Factual background

16. The priority case was presented by Justin Turner QC on behalf of the Claimants and Andrew Lykiardopoulos QC on behalf of AbbVie. The issue raised by the Claimants is whether the applicant for the 656 patent, Abbott Bermuda, was not entitled to claim priority from US 961, because it was not the successor in title to the applicants for US 961, namely Dr Fischkoff, Dr Weiss and Dr Kempeni, who were named as the inventors of that provisional patent filing. In particular, the Claimants allege that AbbVie has failed to prove that, at the date of filing of PCT Application US 2002/017790 ("the PCT Application"), 5 June 2002, Abbott Bermuda was successor in title to the invention the subject of US 961.

17. The parties have, very helpfully, agreed a chronology of events in relation to entitlement to priority, which I attach as an Annex to this judgment. In about 1999 or 2000, the invention the subject of US 961 and of the 656 patent ("the Invention") was made by Dr Fischkoff and Dr Weiss ("the US inventors") and Dr Kempeni. The Invention related to D2E7. On 14 December 2000 Abbott Laboratories agreed to buy BASF AG's pharmaceutical business (known as "BASF Pharma") pursuant to an agreement in writing ("the Purchase Agreement"). The purchase price of BASF Pharma was almost $7 billion, and purchasing the rights to D2E7 was a major driving factor.

18. The pharmaceutical business of the parent BASF company, BASF AG, was not operated by a single legal entity, and the name BASF Pharma was used to refer to the pharmaceutical product-related activities of the various companies within the BASF corporate group including Knoll AG and Knoll Pharmaceutical Company ("KPC"). AbbVie claims that it was BASF Pharma's policy for all rights in the results emerging from its international R&D projects to be held in Germany by either BASF AG or Knoll AG. It further claims that the rights were divided according to the kind of research by which they were generated. Rights arising from basic research were owned by BASF AG. Rights arising from clinical development (such as the Invention) were owned by Knoll AG. Where other companies within BASF Pharma participated in international R&D projects, Knoll AG would reimburse them either directly or through transfer pricing.

19. Following completion of the Purchase Agreement with Abbott Laboratories, on 2 March 2001, all shares in Knoll AG were transferred to Abbott Deutschland Holding GmbH and on 9 March 2001 Knoll AG changed its name to Knoll GmbH. Furthermore, following the completion of the Purchase Agreement the decision was made, as a result of tax planning, for D2E7 rights to be divided between two companies, Abbott Bermuda (for rights outside the US) and Abbott Biotechnology Limited ("Abbott Biotechnology") for US rights. In order to put this into effect, on 29 October 2001 a US Asset Purchase Agreement was made between Abbott Deutschland Holding GmbH and Knoll GmbH as sellers and Abbott Biotechnology as purchaser, and an ex-US Asset Purchase Agreement was made between Abbott Deutschland Holding GmbH and Knoll GmbH as sellers and Abbott Bermuda as purchaser ("the APAs").

20. US 961 was filed by the inventors as applicants on 8 June 2001 (as was required under US law). The PCT Application was filed on 5 June 2002 with the inventors as applicants for the US and Abbott Bermuda as applicant for all other designated states, including the EP region and the GB part thereof. A single claim for priority was made from US 961.

21. The US inventors were both employees of KPC and they both signed Employee's Invention and Secrecy Agreement ("EISAs") with the same terms. The EISAs are to be construed under US law. Dr Kempeni was employed by Knoll AG in Germany from July 1987 until March 2001, when Knoll AG became Knoll GmbH. The law governing Dr Kempeni's employment relationship with Knoll AG/Knoll GmbH was the law of the Federal Republic of Germany, and in particular, the provisions of the German Act on Employee Inventions of 25 July 1957, in the version in effect until 30 September 2009 ("ArbEG").

Chain of title

22. AbbVie's case is that within the BASF Pharma group of companies, equitable title to the Invention was at all material times owned by Knoll AG (later Knoll GmbH). Knoll GmbH then transferred all its ex-US rights to Abbott Bermuda before the filing of the PCT Application. In particular:

    i) The US inventors had entered into the EISAs by which equitable title to any inventions passed to their employer or its nominee. Alternatively, they were employed to invent and under US law equitable title to their inventions was owned by their employer.

    ii) It was agreed between KPC and Knoll AG that inventions (such as the Invention) would be owned by Knoll AG. Accordingly, either under the EISAs or under the "employed to invent" doctrine, Knoll AG was the beneficial owner of the non-US rights of the US inventors.

    iii) The right to claim the Invention from Dr Kempeni, (or the right to claim priority from a first filing made by Dr Kempeni) was held by Knoll AG under German inventor employment law.

    iv) US 961 was filed on 8 June 2001 by the US inventors and Dr Kempeni.

    v) Knoll AG (then Knoll GmbH) transferred all its ex-US rights in the Invention to Abbott Bermuda under an Asset Purchase Agreement dated 29 October 2001.

    vi) The PCT Application was filed on 5 June 2002.

23. Originally, the Claimants alleged that the EISAs failed to assign any equitable interest from the US inventors to their employer, KPC. However, that point was abandoned shortly before the trial. It is now common ground that, pursuant to the EISAs, the equitable interest in the Invention was assigned from the US inventors to KPC. Furthermore, the Claimants alleged that the filing of US 961 triggered the period for Knoll AG to claim the rights of Dr Kempeni under s.6 ArbEG. They contended that

since no claim was made within four months of the filing of US 961 the German rights became the property of Dr Kempeni. That point was abandoned just before closing speeches.

24. Nonetheless, numerous issues remain in relation to the chain of title, in particular between Dr Kempeni and Knoll AG/GmbH; KPC and Knoll AG/GmbH: and Knoll AG/GmbH and Abbott Bermuda.

Legal principles

25. The right to claim priority is provided for by section 5 of the Patents Act 1977, which is declared by section 130(7) to be "so framed as to have, as nearly as practicable, the same effects in the United Kingdom as the corresponding provisions of the European Patent Convention … and the Patent Co-operation Treaty have in the territories to which those Conventions apply."

26. Prior to amendment by the European Patent Convention 2000, Article 87 of the EPC provided:

> "A person who has duly filed in or for any State party to the Paris Convention for the Protection of Industrial Property, an application for a patent or the registration of a utility model or for a utility certificate or for an inventor's certificate, or his successors in title, shall enjoy, for the purpose of filing a European patent application in respect of the same invention, a right of priority during a period of twelve months from the date of filing of the first application."

27. Article 87(1), together with Article 8 of the Patent Cooperation Treaty, give effect to Article 4(A)(1) of the Paris Convention for the Protection of Industrial Property:

> "Any person who has duly filed an application for a patent, or for the registration of a utility model, or of an industrial design, or of a trademark, in one of the countries of the Union, or his successor in title, shall enjoy, for the purpose of filing in the other countries, a right of priority during the periods hereinafter fixed."

28. In *Edwards Lifesciences v Cook Biotech* [2009] EWHC 1304 (Pat); [2009] FSR 27, it was held that, to make a valid claim for priority as successor in title, it was necessary to be a successor in title at the time of filing the application, and a subsequent acquisition of title was not sufficient. Kitchin J said:

> "93 So art.4 [of the Paris Convention] specifies a person is to enjoy a right of priority if he has filed a relevant application for a patent or if he is the successor in title to such a person. Further, any person wishing to take advantage of the priority of such a filing must be required to make an appropriate declaration.

…

> 95 In my judgment the effect of art.4 of the Paris Convention and s.5 of the Act is clear. A person who files a patent application for an invention is afforded the privilege of claiming priority only if he himself filed the earlier application from which priority is claimed or if he is the successor in title to the person who filed that earlier application. If he is neither the person who filed the earlier application nor his successor in title then he is denied the privilege. Moreover, his position is not improved if he subsequently acquires title to the invention. It remains the case that he was not entitled to the privilege when he filed the later application and made his claim. Any other interpretation would introduce uncertainty and the risk of unfairness to third parties. In reaching this conclusion I derive a measure of comfort from the fact that the Board of Appeal of the EPO has adopted the same approach to the interpretation of art.87 EPC in two cases: J-0019/87 and T-0062/05."

29. In *KCI v Smith & Nephew* [2010] EWHC 1487 (Pat), [2010] FSR 31, Arnold J held that "successor in title" included a person who was a recipient of the beneficial interest in the invention in circumstances where he did not own the bare legal interest. Arnold J held at [69] – [71] that that the entire beneficial interest was sufficient to enable the beneficiary to claim priority as a "successor in title". He also held that when determining whether a person is a "successor in title", it must be the substantive rights of that person, and not his compliance with legal formalities, that matter:

> "69 I would add that, even if it was not effective to convey the legal title to the invention, para.3 of the Confidentiality Agreement was plainly effective to transfer the entire beneficial interest in the invention, including the right to file patent applications in respect of it, from Mr Lina to KC Inc. KC Inc would have been entitled to demand that Mr Lina convey the bare legal title to the invention to itself at any time, and to compel Mr Lina to do so if he failed or refused to do it. If necessary, I would hold that that was sufficient to make KC Inc Mr Lina's "successor in title" for the purposes of a claim to priority under art.87(1) of the EPC and art.4(A)(1) of the Paris Convention even if KC Inc had not acquired the bare legal title at the relevant date.
>
> …
>
> 71... Article 4(A) of the Paris Convention and art.87(1) of the EPC are provisions in international treaties whose operation cannot depend upon the distinction drawn by English law, but not most other laws, between legal and equitable title. When determining whether a person is a "successor in title" for the purposes of the provisions, it must be the substantive rights of

> that person, and not his compliance with legal formalities, that matter."

30. This judgment was followed by Birss J in *HTC Corporation v Gemalto SA* [2013] EWHC 1876 (Pat), [2014] RPC 9. Both first instance judgments were considered by the Court of Appeal in *Idenix v Gilead* [2016] EWCA Civ 1089, where Kitchin LJ expressed the provisional view that *KCI* and *HTC* were correctly decided.

31. It is common ground that the correct approach, which was applied by the Court in *KCI* and *Idenix*, is that the issue of which party holds the relevant rights is to be determined in accordance with the law of the transaction which is said to have transferred such rights (in this case US and German law).

Can entitlement to priority be established because all of the inventors applied for the PCT Application?

32. AbbVie's first submission is that it is unnecessary to examine the chain of title because the inventors owned the legal title and made the claim to priority. AbbVie argues that on both parties' cases, when the PCT was filed on 5 June 2002, the inventors each still held legal title to the Invention. Under their EISAs, the US inventors had agreed to assign their rights to KPC or its nominee. This operated as an agreement to assign future rights which needed to be perfected before legal title was assigned. That had not been done by June 2002. Therefore, the US inventors held legal title on trust for KPC or its nominee. In relation to Dr Kempeni, it is common ground that in June 2002 he remained the legal owner of his part of the invention, but the Invention remained an unreported service invention which could be claimed by his employer, Knoll GmbH.

33. AbbVie's case is that in June 2002 the three inventors who filed US 961 and who still owned legal title to the Invention filed a PCT Application claiming priority from US 961. This was permitted under Article 4A of the Paris Convention. Abbott Bermuda was also included as an applicant on the PCT Application. However, AbbVie submits that it makes no difference if there was an additional applicant, provided that the legal owners, who are entitled to claim priority, are applicants for the PCT Application; see *KCI* at [98].

34. I do not accept this argument, for the following reasons. First, I do not consider that Article 4A permits both the original applicant and his successor in title to enjoy a right of priority. In my judgment, where a right to claim priority has been assigned, the assignor cannot subsequently make a claim himself. The Article contemplates a claim to priority either by the original applicant or his successor in title, and not by both. Once the right has been assigned there is no reason why the assignor should retain a right of priority. This is consistent with ensuring certainty as to who is entitled to apply, as referred to by Kitchin J in *Edwards Lifesciences*. Looking at the issue as a question of substance rather than form, in the present case the inventors did not retain a substantive right as of 5 June 2002.

35. Secondly, the PCT Application identifies the inventors as the applicants for "US only" and Abbott Bermuda as the applicant for "all designated states except the US."

AbbVie claims that this makes no difference because, at the time when a PCT application is filed (the point when priority is assessed) it is a single international application. It only later transfers to the national phase. I do not agree. This argument was rejected by Arnold J in *KCI*. In that case, an issue arose as to whether Mediscus was a co-applicant (with KCI) for a European patent, since it was named on a PCT application as the applicant for "GB only". Arnold J found that, since both of the patents in issue were European patents (UK), the only part of the PCT application which was material to the question of entitlement to priority of those patents was the part that related to the European patent. It did not matter whether priority was validly claimed in respect of the United Kingdom national patent.

36. At [84] - [85] Arnold J stated:

> "84 Counsel for S & N submitted that it did not matter whether Mediscus was a co-applicant only for a GB national patent or also for a European patent (UK) since at that stage it was not yet known which of the regional/national phases would be pursued by the applicants. He argued that KC Inc and Mediscus were co-applicants for the PCT Application, and accordingly priority could only be validly claimed in respect of the PCT Application if both co-applicants had the right to claim priority under Article 4(A)(1) of the Paris Convention.
>
> 85 I do not accept that submission. What matters for the purposes of this litigation is whether priority has been validly claimed for the Patents, both of which are European patents (UK), in accordance with Article 87(1) EPC. The PCT is simply a mechanism for the central filing of multiple patent applications. Once an international patent application enters the regional/national phase, it is treated as a regular regional or national application. Accordingly, the only part of the PCT Application that is material to the entitlement of the Patents to priority is the part that relates to the European patent. Provided that priority has been validly claimed in respect of the European patent, it does not matter whether priority was validly claimed in respect of the United Kingdom national patent, if any."

37. By parity of reasoning, it appears to me that the only part of the PCT Application that is material to the priority claim in the present case is the claim in respect of "all designated states except the US". This was made by Abbott Bermuda, and not by the inventors.

38. AbbVie submits, however, that the debate over whether a PCT application is a single international application or a mechanism for the central filing of multiple patent applications is immaterial. It alleges that the reasonable inference to be drawn from the filing of the PCT Application is that the inventors had consented to transfer part of their interest (the right to claim priority for foreign filings) to Abbott Bermuda. The fact that the PCT request was signed by all parties, naming the inventors as applicants

for the US and Abbott Bermuda as the applicant elsewhere is said to be consistent only with such an agreement.

39. I do not accept this argument. By 5 June 2002 all of the inventors had left their employment and none of them had signed the PCT request. I recognise that this request was later replaced by a corrected version filed on 20 September 2002 which included the signatures of the inventors. This replacement was filed within the time-period to correct defects provided by Rule 26*bis* of the PCT Regulations. However, the question that I am considering is a different one. There is no evidence that as of 5 June 2002 any of the inventors had agreed to transfer the right to claim priority for foreign filings to Abbott Bermuda, nor that any of them knew that the PCT request was being filed, as none of the inventors gave evidence. The fact that they may have subsequently agreed to transfer such rights is immaterial. See *Edwards Life Sciences* (supra).

Chain of title from KPC to Knoll AG

40. There is a dispute as to whether the EISAs were effective to transfer equitable title in the Invention from KPC to Knoll AG. This question is governed by US law. In respect of US law, two distinguished experts gave evidence, namely Prof Jay Thomas on behalf of the Claimants and Prof Donald Chisum on behalf of AbbVie. Since 2002 Prof Thomas has been a Professor of Law at Georgetown University, Washington, DC where he has taught courses in patent law, contract law and patent licensing. Amongst other publications, he is one of two co-authors of the treatise "Principles of Patent Law". Prof Chisum was, until 2006, a Professor of Law at Santa Clara University. In 1978 he wrote "Chisum on Patents", a multi-volume treatise on all areas of US patent law. He continues to be the sole author of this work.

41. This issue arises in the following circumstances: The opening clause of each of the EISAs states:

> "I, the undersigned employee, in consideration of my employment by BASF Corporation or any of its affiliates ("BASF"), and of the salary and wages paid for my services in the course of my employment, agree as follows"

It is common ground that "BASF Corporation or any of its affiliates ("BASF")" is a reference in context to KPC because KPC was the affiliate which employed the US inventors. This applies to paragraph 6, which is set out below.

42. Paragraph 6 of the EISAs provides that:

> "6. All inventions, improvements, conceptions, or developments relating to the business, affairs, or fields of interest of BASF which I conceive, make, develop, or complete, either solely or jointly with others, during my employment shall be the property of BASF whether patented or not.

> Upon request of BASF I will execute such (a) patent applications (including divisional, continuing, reissue and extension applications) desired by BASF, and (b) all other documents deemed necessary by BASF to transfer to BASF, its nominees or assigns, all my right, title, and interest in and to such inventions, improvements, conceptions or developments and patent applications and any patents granted thereon including extensions, renewals, and reissues thereof. I will testify in legal proceedings, sign papers, make all lawful oaths and otherwise assist BASF to perfect, maintain, and enforce the same in any country."

43. AbbVie contends that Knoll AG was KPC's nominee to hold all rights resulting from international clinical research and development including the Invention. At any time, Knoll AG could have compelled KPC to transfer legal title. Therefore, as a matter of US law, Knoll AG was the beneficial owner of the US inventors' rights in the Invention. This is denied by the Claimants, who submit that there was no such nomination, nor any enforceable agreement between KPC and Knoll AG concerning nomination or transfer.

AbbVie's case

44. AbbVie contends that at all material times the relevant companies within BASF Pharma operated pursuant to an understanding that all rights in inventions arising from international clinical R&D, including in relation to D2E7, were to be held by Knoll AG. This was not merely some vague intention as to future conduct, but the basis upon which KPC and Knoll AG conducted their businesses.

45. In support of its case, AbbVie relies upon the evidence of the following witnesses:

    i) Dr Gottfried Freier, who was General Counsel of Knoll AG from 1 July 1998 to 31 March 2001, having initially joined BASF AG in 1985. He gave evidence as to the policy within BASF Pharma as to the ownership of rights in inventions operated by the various companies that made up BASF Pharma and how this related to inventions concerning D2E7.

    ii) Prof. Erich Schlick, who was, between 1991 and June 2000, Head of Global Research and Development for BASF Pharma. He sat on the executive board of Knoll AG and was President and Chairman of a US BASF Pharma Company, BASF Bioresearch Corporation. He gave evidence as to the operation of and inter-company coordination within BASF Pharma.

    iii) Dr Melvin Spigelman, who held various senior positions at KPC from 1989 to late summer 2001. He gave evidence as to the relationship between KPC and the rest of the BASF Pharma business, particularly Knoll AG. He also gave evidence regarding the EISAs signed by the US inventors.

46. Each of them explained that the corporate policy within BASF Pharma regarding the Invention (as an invention arising from clinical research on an international R&D

project) was that all rights in it should be held by Knoll AG. As part of this arrangement, Knoll AG reimbursed KPC for all costs incurred in respect of the R&D activities: Freier 1 [9] – [10]; Schlick 1, [7] – [8]; and Spigelman 1, [5] and [7].

47. AbbVie claims that the evidence of these witnesses is supported by certain contemporaneous documents, in particular:

    i) A presentation made in about November 2000 by BASF Pharma management to Abbott prior to Abbott agreeing to purchase BASF Pharma. The slide on page 4 states that Knoll AG "owns the IP developed in clinical research. In addition, it owns the acquired IP and most of the IP which does not relate to basic research".

    ii) A document from the data room to which Abbott was provided access prior to the Purchase Agreement, created in about November 2000. It states that "Roughly, Knoll AG owns the vast majority of the intellectual property pertaining to BASF Pharma" and then lists some exceptions, which are not relevant to this case. It also states that "Since Knoll Pharmaceuticals Corp. is partially involved and participating in development efforts, a reimbursement mechanism has to be and is agreed upon on a case by case basis."

48. No written document relating to the ownership of intellectual property as between Knoll AG and KPC has been disclosed. If such a document existed, and the witnesses did not remember whether this was the case, it has now been lost. However, AbbVie contends that this does not mean that an agreement between the corporations did not exist. The standard practice within BASF Pharma was that agreements (including intra-group agreements) were governed and construed under German law; Freier (1) [19]. German law allows for binding agreements to be concluded orally or in writing; Agreed Principles of German law at Principle 2; Haedicke (2) [36] – [38].

49. As to the relevant principles of US law, Prof Chisum explained that there are no special requirements under US law for a person or company to be nominated under an agreement to be the beneficiary of rights, or for that party to be expressly identified in a contract providing for assignment to a nominee before the agreement can take effect.; Chisum (2) [38]. I accept his evidence.

50. It is agreed that the EISAs are governed by New Jersey law. Prof Chisum explained that, under New Jersey law, an equitable title can be assigned, for example by an inventor's employer, by express written or oral agreement, or by conduct. I accept this evidence. The experts described such an agreement by conduct as an "implied in fact" contract. Prof Chisum elaborated this at [33] – [34] of his first report:

> "33. Accordingly, an equitable interest in a patent, patent application or any interest there is freely assignable. There is no requirement in US law that an agreement assigning equitable title to any interest in a US patent or patent application must be in writing, or must satisfy any other specific formalities.

> 34. The United States Supreme Court's decision in *Standard Parts Co. v. Peck*, 264 U.S. 52 (1924) strongly supports treating this type of equitable title as assignable "by conduct," such as a general transfer of interests in a business. On the facts in *Standard Parts*, an employee working for a first company made an invention and obtained a patent on it. Later, the former employee sued a second company that had acquired the entire assets of the first company. The second company successfully claimed equitable title, which defeated the former employee's suit based on the patent. The Court made no reference to an express written agreement transferring rights from the inventor's employer to the employer's successor (who was a party to an infringement suit and gained an order requiring transfer of legal title to the patent)."

51. Applying these legal principles to the facts, AbbVie alleges that a legally enforceable agreement arose in equity from the facts and circumstances under which the companies operated, and that this is sufficient to vest equitable title in Knoll AG. Alternatively it alleges that the Court would order transfer of equitable title from KPC to Knoll AG because this was in accordance with the parties' mutual understanding, which was that Knoll AG was the nominee of KPC.

The Claimants' case.

52. The Claimants allege that there was no evidence that the US inventors were aware of the policy within BASF Pharma to transfer rights from KPC to Knoll AG when they entered into the EISAs or at any stage prior to the filing of the PCT Application. However, pursuant to paragraph 6 of the EISAs, the US inventors had agreed to transfer their rights, on request of their employer, to any nominee. Their knowledge of the policy is therefore irrelevant.

53. The Claimants allege that AbbVie's evidence goes no further than suggesting that there was a policy within BASF Pharma to transfer rights from KPC to Knoll AG and that does not constitute a legally enforceable agreement. They further allege that there can be no legally enforceable agreement to assign US 961 from KPC to Knoll AG, because the asset had not been valued for tax purposes. Prof Chism did not agree with either of these propositions, and I accept his evidence on this point. As to policy, Prof Chisum explained the point very clearly at 7/987/20:

> "Of course, my view is that if there was the policy equals an implied in fact contract, that will be sufficient. I tried to indicate earlier in my unfortunately lecture-based answer that I look at the equitable title as being linked into the court of equities [sic] power to shape the remedy. The equity is already involved because we hypothetically assume the inventors have refused to transfer legal title. We have equity involved. The question is, "What would be the remedy to whom they order the employee to transfer?" I think even absent under the facts and circumstances here -- I will give you up-front my opinion.

> Even absent what you might call an agreement, the facts and circumstances indicate that KPC designated or nominated Knoll, the German company, and these facts all support the view that there was a nomination, whether or not there was an agreement, between KPC and Knoll."

54. As to the submission that, for there to be a legally enforceable agreement to assign rights, the rights must be valued in the contract, Prof Chisum disagreed at T7/975 –7 and the proposition does not appear in Prof Thomas's evidence. I do not accept the Claimants' submission, which would present great practical difficulties in relation to inventions which had not yet been commercialised.

55. The Claimants rely on the evidence of Prof Thomas, who disputed that there could be an implied in fact contract in the circumstances of the present case on the basis that the implied in fact principle had not been extended in the field of patents beyond the limits of employee inventions. I do not accept this evidence. Prof Chisum explained that implied in fact contracts are not limited to the field of employed to invent and that there is no reason why equitable interests in patents could not be transferred orally or by conduct. The fact that implied in fact contracts normally arise in the context of employee inventions does not mean that the application of the doctrine is limited to this area.

56. The Claimants rely upon a number of documents which they suggest are inconsistent with the proposition that equitable title to the invention of US 961 had been assigned to Knoll AG before the date of the PCT Application. First, the Claimants rely upon an assignment in writing of the interest of the inventors in US 961 to Abbott Biotechnology signed by the US inventors in March 2003. The Claimants allege that this suggests that it was thought in 2003 that the interest lay with the inventors, and no contrary explanation has been provided in evidence. Furthermore, the assignment was not to Abbott Bermuda, the company that AbbVie alleges had the right to claim priority.

57. Secondly, the Claimants rely upon a corrective assignment which was made in November 2014. A recital on page 2 records that:

> "WHEREAS in furtherance of its tax planning and other strategies, Abbott determined to transfer to Abbott Biotech Bermuda all US intellectual property rights related to D2E7 Antibody including all US patent rights, and to transfer to Abbott Labs Bermuda all non-US intellectual property rights related to D2E7 including all non-US patent rights and…executed [the APAs] which provided for the assignment to, respectively, Abbott Biotech Bermuda and Abbott Labs Bermuda, of certain patents and patent applications listed on Schedules to the respective agreements but through inadvertence failed to include the '961 Provisional Application on such Schedule and failed to include KPC as a seller;"

58. The Claimants contend that this shows that the US inventors' interest in US 961 was assigned to KPC and that is where it remained.

59. As to the 2003 assignment, this was after the acquisition by Abbott Laboratories of BASF Pharma, and neither KPC nor Knoll AG were parties to it. Furthermore, by 2003, Abbott Bermuda had ceased to exist, and therefore it is unsurprising that it was not the assignee. The 2014 assignment also post-dated the acquisition by Abbott Laboratories of BASF Pharma. Therefore, neither of them directly concern the relationship between KPC and Knoll AG. Nonetheless, I think that these documents are of some modest assistance to the Claimants. Balancing their probative value against the evidence adduced by AbbVie, and the contemporaneous documents on which it relies, I do not accept the Claimants' case on this issue.

60. The Claimants criticise the evidence of the witnesses called by AbbVie on the basis that they had insufficient personal knowledge of the relevant facts, and suggest that witnesses from the patent departments of the relevant companies ought to have been called. The Claimants allege that the Court ought to have been shown audits of patents or patent assignments relating to patents generally, or in the context of D2E7, to show a pattern of making applications and transferring them to Knoll AG. Finally, they allege that it was not established that the policy was in existence in March 2001. I do not agree. I found the evidence of AbbVie's witnesses clear on this issue. They may not have known every detail, but I was left in no doubt that this was the policy upon which KPC and Knoll AG conducted their affairs, and that this continued to be the policy at the date of purchase of BASF Pharma by Abbott Laboratories.

61. The Claimants submit that the contemporaneous documents relied upon by AbbVie are generalised and of uncertain origin. If any interest had been transferred from KPC to Knoll AG, that would have been recorded, together with the value paid. I do not accept this. In my view, the contemporaneous documents are of some assistance in corroborating the clear recollection of AbbVie's witnesses.

62. Finally, the Claimants allege that reliance cannot be placed on the fact that, according to AbbVie's witnesses, Knoll AG funded the clinical trials which led to the Invention. It is suggested that Knoll AG did no more than contribute to the costs and that no paper trail had been produced of who paid for what. It is suggested that Dr Spigelman was not the best person to provide evidence on this subject. I do not agree. I do not consider that further details are necessary or to be expected, particularly in relation to events that occurred nearly 17 years ago.

Conclusion

63. I find that Knoll AG was KPC's nominee to hold all rights resulting from international clinical research and development, including the Invention. At any time, Knoll AG could have compelled KPC to transfer legal title. Therefore, as a matter of US law, Knoll AG was the beneficial owner of the US inventors' rights in the Invention.

Chain of title from Dr Kempeni to Knoll AG

64. The version of ArbEG which applies is that in effect until 30 September 2009. The ArbEG provides for specific rules on inventions made by employees during the term of their employment. Section 5(1) ArbEG, which concerns the duty to report a service invention, provides that:

> "(1) Any employee making a service invention shall be under a duty to report the invention to his employer immediately in a special written notice indicating that said writing constitutes the report of an invention. Where two or more employees have contributed to making the invention, a joint notice may be filed. The employer shall inform his employee without delay and in writing of the date the report was received."

65. Section 6 then sets out how an employer may claim such a service invention:

> "(1) An employer may claim a service invention by means of an unlimited or a limited claim.
>
> (2) Such claim shall be made in a written statement, addressed to the employee. It shall be made as soon as possible, and no later than four months from the receipt of a proper report (Section 5(2) and (3))."

66. If a claim is not made within the four month period then an employee is free to dispose of the invention pursuant to section 8(2) ArbEG.

67. There is a body of German case law concerning circumstances where a formal report was not made but the employer received sufficient notice of the invention to trigger the commencement of the four month period. The Claimants' main point on this issue, at the start of the trial, was that Dr Kempeni did not formally report the Invention to his employer Knoll AG. The Claimants relied on the decision of the German Federal Court of Justice in *Haftetikett* (BGH GRUR 2006, 754) which held that, in the absence of a formal report, notice will have been given if the employer had sufficient information to file a patent application. The Claimants alleged that the filing of US 961, with Dr Kempeni as one of the applicants, triggered the commencement of the four month period, so that the entitlement of his employer to claim the Invention had passed by the time of the PCT Application.

68. However, at the end of the trial the Claimants abandoned the "*Haftetikett"* point. It is now accepted by the Claimants that no Invention Report (or equivalent) was made under s.5 ArbEG by the time the PCT Application was filed in 2002. Therefore, the time for claiming the Invention from Dr Kempeni had not started to run.

AbbVie's case

69. AbbVie relies on the acceptance by the Claimants that when Knoll GmbH entered into the APA with Abbott Bermuda on 29th October 2001, the Invention had not been formally reported under s.5 ArbEG. Accordingly, legal ownership of Dr Kempeni's

part of the Invention remained with Dr Kempeni, but was subject to the right of his employer, Knoll GmbH, to claim the Invention. Any attempt by Dr Kempeni to assign any rights in the interim would be invalid as against Knoll GmbH. At all material times Knoll GmbH had the right to demand delivery of an Invention Report, pursuant to statute, and to claim the Invention; Agreed principles of German Law 52 and 54-56.

The Claimants' case

70. The Claimants allege that it is only when a claim is made by an employer that the invention, including the right to claim priority, is transferred to the employer. If the employer makes no claim then the right to priority remains with the employee, who may choose to apply for a patent. They allege that, absent a claim by Knoll GmbH under ArbEG, the right to claim priority had not passed from Dr Kempeni, and therefore, the chain is broken. I do not accept this submission. It appears to me that it is based on compliance with formal technicalities, rather than substance. I accept AbbVie's case that at any time Knoll GmbH had the right to demand delivery of an Invention Report, pursuant to statute, and to claim the Invention. Therefore, as in *KCI*, Knoll GmbH had the right to compel Dr Kempeni to transfer the Invention to it. In substance, Knoll GmbH was the owner of the Invention, and could exercise its right to claim it at any time.

Conclusion

71. I find that when Knoll GmbH entered into the APA with Abbott Bermuda on 29 October 2001, legal ownership of Dr Kempeni's part of the Invention remained with Dr Kempeni, but was subject to the right of Knoll GmbH to claim the Invention. Any attempt by Dr Kempeni to assign any rights in the interim would be invalid as against Knoll GmbH. At any time Knoll GmbH had the right to demand delivery of an Invention Report, pursuant to statute, and to claim the Invention. Therefore, Knoll GmbH was, in substance, the owner of the Invention.

Transfer of rights from Knoll GmbH to Abbott Bermuda

72. This issue arises because the APA which transferred non-US assets to Abbott Bermuda failed to list US 961 in the schedule which purported to identify such assets.

Background

73. The background to the APAs is described by Mr Poulos at [42] - [46] of his statement. Mr Poulos has held a number of positions at Abbott Laboratories/AbbVie Inc since he joined in 1978. From 2000 to 2005 he was Division Vice President of the Licensing and New Business Development Group, which was responsible for the assessment and subsequent acquisition of BASF Pharma.

74. According to Mr Poulos, after Abbott had acquired BASF Pharma in March 2001, the business was restructured with a view to integrating it into the Abbott business in a tax efficient manner. This restructuring plan involved transferring all D2E7 assets to two newly-created Bermudan companies. All US IP assets and rights were to be

transferred to Abbott Biotechnology and all ex-US IP rights and assets were to be transferred to Abbott Bermuda.

75. AbbVie also called Ms Linda Gohlke, who is an Attorney who has worked as an independent contractor for the corporate law departments of Abbott/AbbVie since 1998. She was tasked with creating the two Bermudan companies and preparing the APAs to transfer the rights in D2E7 to those companies. Her evidence was that the aim was to transfer all D2E7-related intellectual property rights that existed at the date of closing of the transactions. In order to identify the patents and patent applications to be transferred, Ms Gohlke referred to two documents that were created before US 961 and therefore did not list it: the Patent and Patent Application Assignment and Agreement dated 2 March 2001 and Exhibit 5.1 to the Purchase Agreement.

76. In both APAs, Article 1 defines the "D2E7 Assets" as "the assets relating to D2E7 listed on Schedule 1 and Schedule 2" but the content of their schedules is different: Schedule 1 of the US APA contains a "List of United States Patents and Patent Applications for D2E7" whereas Schedule 1 to the ex-US APA contains a "List of Patents and Patent Applications for D2E7 (excluding the United States)". Both Schedule 2s contain the same list of five agreements but the introductory paragraphs distinguish between US and non-US rights as appropriate.

77. The sellers in each case were both Abbott Deutschland Holding GmbH and Knoll GmbH. The purchasers were Abbott Biotechnology for the US APA and Abbott Bermuda for the ex-US APA. They include a Preamble which indicates an intention on the part of the sellers to sell all assets relating to D2E7:

> "Sellers desire to sell the rights and assets related to a recombinant fully human therapeutic antibody (hereinafter called D2E7) …"

78. However, Article 1 of the APAs (and in particular the ex-US APA) states that:

> "Subject to the terms and conditions of this Agreement Sellers hereby agree to sell and deliver to Purchaser at the Closing (as hereinafter defined) all of their interest in the assets relating to D2E7 listed on Schedule 1 and Schedule 2 (the "D2E7 assets"). Purchaser hereby agrees to purchase and accept at the Closing the D2E7 assets."

79. US 961 was not included in the Schedules.

German principles of contract construction

80. The ex-US APA is to be construed and governed in accordance with German law, pursuant to Article 12G. AbbVie relied on the evidence of Prof Haedicke and Prof Trimborn, and the Claimants relied on the evidence of Prof Leistner. They are all expert German lawyers with very significant expertise in patent law.

81. The experts were able to agree many of the principles of German law. Under German rules of contract construction:

i) When a declaration of intent is interpreted, it is necessary to ascertain the true intention rather than adhere to the literal meaning of the declaration.

ii) The issue of contractual interpretation is a question of law to be determined in the light of the facts agreed by the parties and findings as to any disputed facts. No burden of proof applies to questions of law.

iii) Contractual interpretation is first a subjective and secondly an objective exercise.

iv) The contract is construed by ascertaining the subjective intent of the parties. If the parties had deviating intentions, then objective interpretation is applied.

v) The concordant subjective intention of both parties is of primary importance for the contract interpretation and supersedes the wording of the contract. This is true in cases in which the concordant intention of the parties deviates from the objective wording of the contract. In these cases the concurring intention of the parties is the decisive element. Objective contract interpretation and inference of reasonable intentions in good faith play no part in this form of contract interpretation.

vi) The words used in the contract will be assumed to be correct and exhaustive but this assumption is rebuttable.

vii) Extrinsic evidence (including both pre- and post-contractual materials) is admissible to interpret a contract.

viii) If no concordant subjective intention of both parties can be identified, objective contract interpretation applies.

ix) With contracts between members of the same corporate group it may be easier to identify a concordant intention which supersedes and/or assists in interpreting the wording of the contract.

82. The experts agreed that the intention of the parties must be judged at the time the contract was made (although post contract evidence is admissible to do this). They also agreed that the German Courts will not come to the aid of a party that has made an agreement which, with hindsight, it would want to have made differently.

AbbVie's case

83. AbbVie submits that the evidence is clear that the concordant subjective intention of the parties at the time that the APAs were entered into was to transfer all ex-US rights in D2E7 to Abbott Bermuda, and all US rights in D2E7 to Abbott Biotechnology.

84. In particular, it relies on the evidence of Mr Poulos and Ms Gohlke to establish the following: The intention of the parties was to transfer all D2E7 rights including the rights in the Invention to the two Bermudan companies. Although US 961 was not explicitly listed in the Schedules to the APAs, the purpose of the Schedules was not to exclude any IP relating to D2E7 from the agreements but to distinguish between US

and ex-US assets. Furthermore, the purchase of the rights in D2E7 was a significant factor for Abbott Laboratories in the purchase of BASF Pharma and the group decided to move those rights to the Bermudan companies following the purchase. It would undermine this objective to leave some D2E7 assets to be held in Germany.

85. In addition to its evidence of fact, AbbVie contends that contemporaneous documents corroborate the fact that the parties intended Abbott Biotechnology to acquire all US D2E7 rights and for Abbott Bermuda to acquire all ex-US D2E7 assets. This is shown by certain Research and Development Agreements entered into immediately after the APAs, which stated in the recitals:

> "A. Abbott Biotechnology has acquired from [Abbott GmbH & Co KG]… all rights in the United States to a pharmaceutical compound commonly referred to as D2E7 (the "Compound")
>
> B. [Abbott Laboratories (Bermuda) Ltd] has acquired from [Abbott GmbH & Co KG] all rights to the Compound in territories outside the United States."

86. AbbVie also relies on the evidence of Mr Poulos that ensuring that all rights were transferred was particularly important for tax reasons. The consequence of not transferring later-expiring patents (such as the PCT Application) which become crucial after the expiration of the compound patent, would be that the chosen tax strategy would terminate upon the expiration of the compound patent. This was contrary to the aims of all parties to the APAs.

87. Given this subjective intention, under accepted principles of German law, the rights of the US inventors in the Invention held by Knoll GmbH passed to Abbott Bermuda, which became successor in title in equity to the Invention from the US inventors. The same is true in relation to the rights originally held by Dr Kempeni, which I consider in more detail below.

The Claimants' case

88. The Claimants contend that, even on AbbVie's case, there is a break in the chain of title. The purpose of the APAs was to transfer only ex-US assets to Abbott Bermuda. If there had been intention to include US 961 in these agreements, it would have been recognised as a US asset and consequently would have been assigned to Abbott Biotechnology. However, it is necessary to have regard to the conclusion of Kitchin J in *Edwards Lifesciences* at [93], when considering Article 4A of the Paris Convention, that "successor in title" means "successor in title to the invention". In my judgment, the Claimants' submission confuses rights in the Invention, including the right to claim priority, with rights in US 961. US 961 was a United States patent application. However, this does not prevent the parties to the APAs from agreeing that all rights in inventions relating to D2E7 outside the United States should be transferred to Abbott Bermuda.

89. The Claimants submit that the objective interpretation of the ex-US APA is clear. It is an agreement to assign assets listed in the Schedules and Article 1 does no more than

that. I agree with this, as a matter of objective interpretation. Had this been a question of interpretation of contract under English law, I would have found that the ex-US APA transferred only the assets relating to D2E7 listed in Schedule 1 and Schedule 2 and I would then have considered whether rectification was appropriate. Given that this case is to be decided under German law, the approach is different. The concordant subjective intention of both parties is of primary importance and supersedes the wording of the contract. Where the concordant intention of the parties deviates from the objective wording of the contract, concordant subjective intention of the parties is the decisive element.

90. As to concordant intention, the Claimants submit that AbbVie has failed to prove the relevant facts. It contends that numerous other witnesses could have been called, who would have had better knowledge of the facts than either Mr Poulos or Ms Gohlke. For example, the ex-US APA was signed on behalf of Abbott Bermuda by Thomas Freyman and on behalf of Abbott Deutschland Holding GmbH by Wolfgang Oppermann, neither of whom was called to give evidence. Furthermore, neither of the signatories to the agreement from Knoll AG were called to give evidence and no pre-contractual documents have been disclosed which show that Knoll AG intended to assign the rights to US 961 to Abbott Bermuda.

91. As to Ms. Gohlke, she was working on instructions from the tax department and was not a patent or tax expert. No-one complained that her drafts of the APAs did not give effect to the intention of the respective parties. Ms. Gohlke did not personally prepare the Schedules. To the best of her recollection someone from the patent department did. But no one from either the tax department or the patent department was called to give evidence on behalf of AbbVie.

92. As to Mr Poulos, the Claimants submit that he was not in a position to assist on the detail of the arrangements about which he gave evidence. He did not profess expertise in law or tax affairs and he depended on the tax department for advice. He did not personally receive the tax department's advice and could not recall seeing it, although he was quite clearly aware of its conclusions. Furthermore, he was not involved in the preparation of the APAs.

93. I do not accept the Claimants' submission in this respect. It was not necessary for Mr Poulos to have expertise in patent or tax law, nor to have personally received the tax department's advice, nor to have been involved in the preparation of the APAs. His evidence about the concordant intention of the parties was clear and convincing, and I accept it. I agree that Ms. Gohlke's recollection of events that took place many years ago was, understandably, somewhat limited. Her evidence is of some assistance, insofar as it corroborates the evidence of Mr Poulos.

94. A separate point arises in relation to the rights originally held by Dr Kempeni. The Claimants allege that the right to compel an inventor to provide an Invention Report and then to claim the invention is not transferable under German law. Therefore, even if Knoll AG/GmbH was entitled to compel Dr Kempeni to transfer his rights in the Invention, this could not be transferred to Abbott Bermuda. Whilst there was some debate between the German experts about whether the right to claim an employee

invention was transferable, I accept Prof Leistner's view, that the prevailing opinion under German law is that the right to claim an employee invention is not transferable.

95. However, Prof Trimborn explained at [3.1] of his second report that:

> "… the legal effect of a claim to the invention (s. 6, 7 ArbEG old version) only relates to the right in the invention, and the assignment of property rights themselves is not covered by it. The transfer of property rights requires a separate act of assignment, as Prof. Leistner correctly notes (loc. cit. 6.12 of his report). This assignment is made according to the provisions of s. 298 ff. of the Civil Code ("BGB") which concern the assignment of claims.
>
> The same applies to the right of priority which arises due to a property right application and which accrues to the applicant. The right of priority itself is independent of the substantive-law entitlement of the applicant, and can be assigned informally (and also implicitly), independent of the property right. The Federal Supreme Court explicitly stated this in its Fahrzeugscheibe decision of 16 April 2013 – X ZR 49/12 and this is undisputed."

96. I accept this evidence. Accordingly, this issue does not affect the ability to transfer the right to claim priority after a patent has been filed. In addition to the right to claim the invention, the employer also has the right to claim priority from any first filings and can transfer that right.

97. Furthermore, when the PCT Application was filed Knoll GmbH had agreed to transfer all its ex-US rights in US 961 to Abbott Bermuda. Even though the right to compel an Invention Report and then claim the Invention from Dr Kempeni was not transferrable, it could be exercised by Knoll GmbH. At any time after the APA and prior to the filing of the PCT Application, Abbott Bermuda could have compelled Knoll GmbH to claim the Invention from Dr Kempeni and then to transfer it to Abbott Bermuda.

Conclusion

98. In my judgment, AbbVie has proved that, at the date of filing of the PCT Application on 5 June 2002, Abbott Bermuda was "successor in title" to the invention the subject of US 961. I have accepted AbbVie's evidence concerning its chain of title, which is credible, and makes a great deal of commercial sense.

The technical case

The administration of the Claimants' proposed products at a dose of 40mg sc every other week for the treatment of RA

The expert witnesses

99. The Claimants and AbbVie relied on expert evidence on RA from Prof Jonathan Edwards and Prof Janet Pope and expert evidence on pharmacology from Professor Atholl Johnston and Professor Alan Boddy, respectively. All of these witnesses are at the top of their professions.

Prof Edwards

100. Prof Edwards is Professor Emeritus in Medicine at University College London. He retired from clinical practice in July 2010, but remains involved with research in the field of RA and provides consultancy services and advice on the use of biologic therapies in RA. Throughout his career, Prof Edwards focused on both clinical and research-based rheumatology with an emphasis on RA. Since 1990, he has also been involved in the development of a number of biologic therapies for the treatment of RA. Throughout his rheumatological career of some 30 years, he maintained a clinical practice, predominantly in RA and other forms of inflammatory arthritis.

101. Prof Edwards worked on a number of investigations into potential biologic therapies for treating RA. From 1990-1992, he was involved in collaboration with Celltech conducting pre-clinical studies of a murine anti-TNFα antibody known as CB6. This involved studies on the localisation of TNFα in human tissue. In 1995, he was a clinical investigator in a Phase II study, in collaboration with Roche Products, of a TNFα receptor fusion protein, known as lenercept.

102. In 1996, Prof Edwards became aware of the antibody rituximab, which depletes B cells by binding to CD20, an antigen present on the surface of the B cells. In 1997, rituximab was licensed for use in B cell lymphoma and by October 1998 Prof Edwards had set up a small trial of rituximab in five RA patients, followed by a 22 patient study in about August 1999. In these studies, he investigated a number of doses and dosing intervals (including single doses, weekly dosing and dosing in alternate weeks), with and without the use of other known therapeutic drugs, such as cyclophosphamide and corticosteroids. In a subsequent study in collaboration with Roche Products, rituximab was administered in two doses, two weeks apart, with and without co-administration of methotrexate.

103. The use of rituximab to treat RA was a different approach to the treatments that had preceded it in that it attacked B cells with a short, sharp shock, rather than utilising a maintenance regimen. Prof Edwards' work in relation to rituximab was extremely valuable. Prof Pope said that it had changed the practice of RA therapy greatly.

104. AbbVie made a number of criticisms of Prof Edwards' evidence. First, Mr Tappin QC, who presented this part of the case on behalf of AbbVie, alleges that there were some errors in Prof Edwards' reports and oral evidence. For example, it is said when he came to give evidence he affirmed [69] of his second report which claimed that an

abstract known as Rau (907) was not a double dummy study, even though he had already decided that this was incorrect, as he explained during cross-examination. AbbVie claims that this showed a lack of care in some aspects of his evidence. I do not accept this submission, and I consider the errors to be trivial, of the type that will inevitably emerge during a long cross-examination. I would certainly not describe his evidence as careless.

105. Secondly, it is alleged that he approached the case on the basis that the rheumatologist in the skilled team was someone of the calibre of himself, or Prof. Maini, or Dr Weinblatt, all of whom were world leaders in the field. This put the level of skill of the unimaginative skilled person far too high. I reject this submission. Prof Edwards explained that the number of skilled rheumatologists engaged in investigating dosage regimens for new RA drugs in 2001 was small, about 50 in academia and a similar number in industry. Therefore, when asked to identify the skilled person, he considered that this notional construct would have been one of those individuals who was actively interested in the field at the relevant date. The real question is whether, when assessing the question of obviousness, he was aware of, and applied the standard of, the unimaginative skilled person. I am satisfied that he was aware of the standard, and did apply it, to the prior art which he was asked to consider.

106. Thirdly, it is alleged that he tended to see things through the lens of rituximab, on which he had done so much work and which was a very different treatment to maintenance therapies, and that he was not as focused as others in the field would have been on TNFα inhibitors. I do not accept this submission. I was in no doubt that Prof Edwards knew a great deal about TNFα inhibitors, both now and in 2001, and was in no way distracted by his work on rituximab when considering the issues in this case.

107. Fourthly, it is said that Prof Edwards had considerable expertise in pharmacology as well as rheumatology. This led him to the view that the rheumatologist would not need assistance from a pharmacologist. Whilst I consider that the team would have the skill-set of a rheumatologist and a pharmacologist and that those skills might or might not be embodied in a single person, I do not see how this in any way affects the weight that I should give to Prof Edwards' evidence.

108. Fifthly, Prof Edwards drew attention to the fact that when he was given the cited prior art, he was aware of the approved dosing regimen for Humira. It is said that he accepted that he was using hindsight. As I understood his evidence, he accepted, very reasonably, that some degree of hindsight was inevitable as a matter of generality, but in the present case I formed the clear view that he was able to exclude it from his consideration of the issues.

109. Sixthly, it is said that Prof Edwards accepted that his view had been formed on the basis of the cited prior art without taking into account additional prior art relied on by AbbVie (which he accepted the rheumatologist would have found and read) and that his later assessment of the additional prior art involved looking for consistency with the view he had already formed. I do not consider that this fairly characterises the totality of his evidence. When he was asked to consider the additional prior art,

selected by AbbVie, he explained in some detail why it did not change his view and provided compelling technical reasons to support this.

110. Seventhly, when pointing to inherent bias in open label studies, Prof Edwards explained that there was a tendency for patients to ask for a higher dose because, even if they were responding, if it seemed to work, more might work better. He explained that clinicians and nurses tended to adhere to such requests, even if not in the clinical trial protocol, as they were sympathetic to patients. It is submitted that this evidence was wrong, and reflected his relatively limited experience of clinical trials. I reject this submission. The evidence struck me as highly convincing, based on Prof Edwards' very considerable experience of clinical practice.

111. Prof Edwards could see both sides of almost every question, and, on occasion, was anxious to agree with the cross-examiner, in circumstances where, if he had had more time to reflect, he might have given a somewhat different answer. However, this made him a very fair witness, and lent weight his evidence on issues on which he stood his ground, and was not prepared to agree. Overall, I consider that Prof Edwards was an excellent witness. He had good technical reasons for his conclusions and was completely frank and unbiased.

Professor Pope

112. In 1993 Prof Pope became a consultant rheumatologist at the Department of Medicine, Victoria Hospital, London, Ontario, a position she held until 2000. Since 2005, Prof Pope has been Professor of Medicine and Chair of the Division of Rheumatology at Western University in London, Ontario, Canada. She is also Professor of Epidemiology and Biostatistics at Western University. She has been a practising rheumatologist for over 20 years and is the Chief of the Rheumatology Centre at St. Joseph's Hospital in London, Ontario, where she is responsible for over 1000 patients with RA.

113. She has been actively involved in the conduct of many clinical trials including a number of studies into the effects of biologic therapies for the treatment of RA. She was involved with trials of adalimumab including the trial known as DE011, published in 2004.

114. The Claimants made a number of criticisms of Prof Pope's evidence. First, Mr Waugh QC submitted that in spite of her research experience, she approached the issues in this case from the perspective of the prescribing rheumatologist. She expressed a strong preference for personalised medicine, which could be tailored to meet the needs of patients on an individual basis. This is not, in fact, a criticism. Rather, it is an ideal goal, showing an admirable desire to improve the condition of every patient. However, I accept that this does not reflect the approach of the notional, unimaginative rheumatologist involved in the development of dosage regimens for D2E7. I accept the evidence of Prof Edwards, that the skilled clinician would be looking for a dosage regimen which would help the condition of the majority of patients, having regard also to cost considerations, patient convenience and, accordingly, patient compliance. This may explain why Prof Pope suggested two obvious dosage regimens in the light of Kempeni 1999 and Kempeni 2000, which

were very different from the proposals set out in those documents, and would have required the skilled reader to reject the approaches set out by world-leading RA clinicians, and substitute his own views on dosing regimens.

115. Secondly, the Claimants point out that Prof Pope has provided evidence for AbbVie in parallel proceedings in the European Patent Office in respect of the 656 patent, before it was revoked at the behest of AbbVie, in the United States Patent and Trademark Office, and in the Canadian Patent Appeal Board. She was very familiar with AbbVie's case in relation to the dosage regimen claimed in these patents, having been involved closely with AbbVie's various legal teams from around the world for a number of years. In the light of this, it is said that Prof Pope's evidence was not as objective as that of Prof Edwards, and led her to try to defend extreme propositions, and to avoid direct answers to direct questions. It is also submitted that she failed to draw attention to material facts in her reports, which contradicted important parts of her evidence.

116. I approach this submission with caution. The Patents Court is privileged to be educated in technical issues by leading experts, and generally such evidence is of great value. If an expert does not agree with the case advanced by the client, he or she will not be instructed. If an expert concedes a point in cross-examination, that concession will be seized upon by the opposite party, either as evidence of inconsistency, or as conceding a key point in the case. There is nothing wrong in instructing the same expert in several jurisdictions, who may thereby gain a greater awareness of the weaknesses, as well as the strengths, of the case which he/she is supporting.

117. On the other hand, it is vital that experts comply with the duty to be objective, to point out weaknesses in the case that they support, and to recognise that their first duty is not to their client, but to the Court. Prof Pope's first report explains that, as one would expect, she had been properly instructed in these matters by Herbert Smith Freehills. However, it is not merely a question of an expert stating that he/she has read and understood the relevant duties. Rather, the expert needs to adhere to them strictly. This is likely to involve careful additions and alterations by the expert to draft reports, which are often worked on by many hands. Furthermore, if, during cross-examination, it becomes clear that some part of the expert report is mistaken, it is necessary to say so, rather than doggedly to adhere to the party line.

118. In the present case, I should make it clear that I do not consider that Prof Pope was deliberately trying to mislead the court. She had convinced herself that her evidence was justifiable and was articulate in her attempts to justify it. However, unlike Prof Edwards, I do not consider that she was able to see the opposite side of the picture, or, on occasion, to deal properly with questions arising from her evidence, preferring not to give a direct answer to the question, or to say that she would pass it over to the pharmacologist. I am also concerned about the failure to mention in her reports that she had worked on a biologic for the treatment of RA known as anakinra, the history of which contradicts material parts of her evidence. I am prepared to accept that this was a mistake, rather than a deliberate omission, but it should not have happened.

119. Thirdly, the Claimants submit that, in the end, Prof Pope effectively conceded obviousness and agreed with Prof Edwards. On the contrary, in my judgment, when considering the totality of her evidence, she stuck to her position throughout, where, on occasion, it would have been better to concede points.

Prof Johnston

120. Prof Johnston is a Professor of Clinical Pharmacology at Barts and the London School of Medicine and Dentistry. He has been involved with the design and execution of clinical trials for approximately 40 years, since 1977. He has advised extensively on the set-up of such trials, including the pharmacokinetic aspects of the studies and on the analysis of the drug concentrations in bodily fluids. Since 1999, he has run a Masters course at Barts in Clinical Drug Development. He has also taught pharmacokinetics to medical undergraduates since the 1980s, and to Medical Sciences and Clinical Medical Microbiology students since the 1990s.

121. No personal criticisms of Prof Johnston are made by AbbVie, and I found his evidence to be clear and fair. AbbVie's analysis of his evidence goes to certain important issues in the case, which I consider later in this judgment.

Prof Boddy

122. Prof Boddy is Professor of Pharmacy (Cancer Therapeutics and Personalised Medicine) in the Faculty of Pharmacy at the University of Sydney. Prof Boddy's primary area of expertise is in the application of pharmacokinetic and pharmacodynamic principles to the dosing of drugs, including the clinical development of drugs and the design of dosage regimens in relation to cancer. The work that he has done is extremely valuable.

123. In 1993 Prof Boddy began work at the Cancer Research Unit at Newcastle, where, from 1996 he was a lecturer. In 2006 he became Professor of Cancer Pharmacology at the National Institute of Cancer Research. In 2014, he emigrated to Australia and took up his current position at the University of Sydney. He was a founding Chairman of the Pharmacology Group of the UK Children's Cancer Study Group in 2000, a position that he held until 2009. Particular areas of research included optimisation of established treatments and the safe administration of high dose chemotherapy regimens, with a focus on pharmacologically guided drug therapy in infants and very young children.

124. No personal criticisms were made by the Claimants about the way in which Prof Boddy gave his evidence. As with Prof Johnston, I consider that he gave his evidence clearly and fairly. Prof Johnston suggested that the difference of opinion between them could be attributed to the fact that they approached the issues from different perspectives. Prof Boddy was looking at the matter from the position of a pharmacologist with great expertise in cancer, whereas Prof Johnston was approaching the issues from the perspective of a general pharmacologist. Because cancer is a life-threatening disease, his view was that the approach was very different when considering dosage regimens for RA. He explained the approach in relation to RA during his cross-examination (3/334/6-21):

> "When I am advising people about developing a drug, what we are trying to do in a chronic disease like rheumatoid arthritis is we are trying to get a dose that will be effective but is not necessarily the maximum dose. It will not necessarily be effective in all patients. The idea is to get an effective dose that is going to be used to begin therapy and of course if there is failure of therapy, you then have the option of increasing the dose. If you give everyone the maximum dose that you have got side effects or adverse events, you cannot cut back in the same way. What you need to do is start low and work up, and you have that option. That is what you are trying to do; you are trying to get an effective dose that will look at the majority of patients, but will not be effective in all patients."

125. I accept this evidence. Cancer treatment, however, involves different considerations. As Prof Boddy accepted, in cancer treatment there was generally a narrow therapeutic window so that dosing had to be approached with considerable caution. As a result, individual dosing matched to the individual's weight or surface area was much more common, as was the tendency to titrate downwards (rather than upwards as in RA).

126. AbbVie submits that it is not necessary to have experience in the design of dosage regimens for the treatment of RA, as neither of the pharmacologists had such experience. I accept this, and I also agree that Prof Boddy was well qualified to address the issues arising in the present case. However, I bear in mind that Prof Boddy's view was that there was not enough information in the prior art to allow a pharmacologist to come up with any reliable prediction of whether any other regimen would produce safe and efficacious plasma concentrations over the course of the dosing regimen, in spite of the fact that the prior art reported the results of small scale clinical trials on hundreds of RA patients, and was extremely encouraging about the results.

127. I consider that a reasonable explanation for the differences of opinion between Prof Boddy and Prof Johnston is that they come from different backgrounds. Prof Johnston is a general pharmacologist, whereas Prof Boddy has many years of experience in cancer treatment. I believe that he has approached this case by applying that experience.

The skilled person

128. There was a lively, but ultimately pointless, debate between the parties about the identity of the skilled person. It was common ground that the rheumatologist would lead the team. The Claimants' case is that the rheumatologist would have an understanding of pharmacology, including dose response relationships, and would have access to the input of a clinical pharmacologist as needed. In later stages of drug development and in using an existing therapy in a new indication, it is less likely that the rheumatologist would consult a clinical pharmacologist. AbbVie's case is that the skilled team would have involved a pharmacologist who would be consulted by the rheumatologist on pharmacological issues.

129. The reason why the debate is pointless is because what matters is the skill-set of the team, not whether that skill-set is to be found in one or two individuals. I accept AbbVie's submission that the skilled team would be led by a rheumatologist, and would have pharmacological expertise, whether by consulting a pharmacologist or as part of the skills of the rheumatologist.

Technical background

130. The parties acknowledged that much of the common general knowledge was common ground between the expert rheumatologists and pharmacologists. However, when it came to the detail, the parties were unable to agree. I was sent tables setting out the relevant expert evidence on various issues, from which I have prepared a technical background to this case. I find that the information set out in this section was common general knowledge at the priority date.

Background issues relating to rheumatology

Rheumatoid Arthritis

131. RA is a chronic and progressive autoimmune inflammatory disease where the body produces autoantibodies (antibodies against the body's own tissues). There are two major subgroups of arthritis – osteoarthritis and inflammatory arthritis. In osteoarthritis, the central process is the mechanical failure of cartilage and reactive overgrowth of bone. By contrast, in inflammatory arthritis either the synovial lining of joints or ligamentous insertions (or both) become inflamed as a result of immune system malfunction. As inflammatory arthritis progresses, the malfunctioning immune system attacks tissue in and around the joint, leading to inflammation, pain, stiffness and ultimately erosion of bone and cartilage. As there is no cure, long term treatment is usually required. References to "arthritis" in this judgment are to inflammatory arthritis.

132. Two of the most common types of inflammatory arthritis, which together make up around 80% of cases, are RA and psoriatic arthritis. I have limited the technical background section to issues relevant to the treatment of RA, as this is the only substantial technical aspect which is still in dispute. In RA, inflammation typically occurs in the synovial tissue lining the internal surfaces of synovial joints. Synovial joints affected are usually the small joints of the hands and feet, ankles, knees, hips, shoulders, wrists and elbows. The autoantibody in RA is known as rheumatoid factor, the presence of which is part of the usual disease criteria for RA.

Measuring disease activity: ACR and DAS scoring

133. By the priority date, two scoring systems for measuring disease activity were commonly used in clinical trials: the American College of Rheumatology ("ACR") improvement measures, and the European League Against Rheumatism Disease Activity Score ("DAS"). The former is a relative measure of improvement against an earlier baseline, whereas the latter is an absolute measure of disease activity.

134. In order to achieve an ACR20, the patient must achieve a greater than or equal to 20% reduction in the number of swollen joints ("SJC" or "SWJC") and the number of

tender joints ("TJC"), and also at least 20% improvement in three of the following five measures of RA:

i) Levels of an acute phase reactant, either Erythrocyte Sedimentation Rate ("ESR") or C-Reactive Protein (blood markers of inflammation, measured from the patient's blood);

ii) Patient's global assessment of disease activity;

iii) Physician's global assessment of disease activity;

iv) Patient's assessment of pain; and

v) Patient's assessment of physical function.

135. ACR50 and ACR70 are higher response thresholds, respectively requiring a 50% improvement and 70% improvement according to the above-described criteria. When reporting the data for a cohort of patients, it is standard practice to display the ACR values in a cumulative manner. For instance, the number of patients reported as achieving an ACR20 response will include patients that achieved an ACR20 response or better (i.e. this includes patients who also achieved ACR50 and ACR70).

136. To calculate the DAS, the following are measured: SJC and TJC; levels of ESR; and a patient global health assessment. The results are then fed into a mathematical formula to produce the overall DAS. DAS is scored on a continuous scale, with higher numbers indicating greater disease activity. The level of disease activity can be interpreted as low ($\leq$ 2.4), moderate (2.4 $\leq$ 3.7, or high (> 3.7). A DAS < 1.6 corresponds to a state of remission. Patients with DAS scores at around 5.5 would have severe disease activity. Commonly, a change in DAS of 1.2 was considered to be a significant change.

History of the treatment of RA

137. Prior to 1950, aspirin (an anti-inflammatory analgesic) was the mainstay in treating inflammatory arthritis. In 2001, both anti-inflammatory agents and simple analgesics were still commonly used for symptomatic relief (e.g. ibuprofen and diclofenac). Simple analgesics only reduce the pain associated with arthritis, whereas anti-inflammatory analgesics reduce short-term swelling from fluid accumulation in inflammation (oedema) though not chronic swelling from immune cell accumulation or tissue damage.

138. When a patient's disease progressed (with an increase in irreversible joint erosion), more aggressive drug therapies, known as disease-modifying anti-rheumatic drugs ("DMARDs"), were added to the treatment schedule. DMARDs were known to be capable of interrupting the pathological progression of RA, reducing the rate of joint damage (if only modestly), rather than merely ameliorating pain. However, DMARDs were historically perceived as being too toxic to warrant use at the outset of the RA diagnosis, when symptoms of the disease were less severe.

139. By 2001, the preferred DMARD for treating RA for most physicians was methotrexate (or "MTX") (given orally, usually in a dose of between 10 and 25mg weekly). Methotrexate was originally used in oncology and as an immunosuppressant after transplantation. Amongst immunosuppressives, it was known to be inexpensive, relatively safe and reasonably well tolerated, at least at lower doses, with the most commonly reported side effect being nausea. Methotrexate became more widely used in the 1980s, with the recognition that RA had an immunological basis and that immunosuppressants were likely to slow disease progression. By 2001/2002, the majority of RA patients receiving DMARDs were receiving methotrexate. Roughly one third of patients were not able to take MTX due to either lack of efficacy or (more often) intolerance to the drug (the proportion remains the same today).

140. Other DMARDs in standard practice in 2001 were hydroxychloroquine and sulfasalazine, which were well tolerated but relatively weak DMARDs, and leflunomide. These were primarily used as alternatives for patients not responding adequately to, or unable to tolerate, methotrexate. In the 1990s, it became more common for rheumatologists to treat patients using a combination of DMARDs. Studies had shown the additive potential of combining certain DMARDs, and controlling the disease improved long-term outcomes.

The role of TNFα and the development of anti-TNFα biologic therapies

141. By the early 1990s, although a number of potential targets had been investigated, one pro-inflammatory cytokine (small signalling proteins important in the immune system), tumour necrosis factor α (TNFα), was increasingly suspected to play a key role in inflammatory joint disease, and it became a key therapeutic target as a biologic therapy.

142. A biologic therapy is a drug that is manufactured in, extracted from, or synthesised from biologic sources. They include fusion proteins (recombinant proteins often comprising a human receptor protein which binds to a specific target in the body linked to another protein which may, for example, impart stability) and monoclonal antibodies (custom made antibodies designed to bind to a specific target in the body). By the priority date, two anti-TNFα biologic therapies had obtained regulatory approval in (for example) the USA, Canada and Europe for the treatment of RA. These were infliximab (trade name Remicade), a monoclonal antibody, and etanercept (Enbrel), a fusion protein. The results of the key clinical trials for both of these drugs were widely reported in the RA research community.

Infliximab

143. Infliximab (also known in the rheumatology literature as "cA2") is a chimeric anti-TNFα monoclonal antibody (described as a chimeric antibody because it is manufactured as a part human part mouse antibody). By the mid-1990s, the rheumatologist would have been well aware of cA2 and very familiar with the work of Professors Feldman and Maini of the Kennedy Institute, who published studies on trials they conducted.

144. Infliximab was licensed for the treatment of RA in the US in November 1999 by the FDA, and in Europe by the European Medicines Agency in June 2000. Both regulatory agencies licensed infliximab for use in combination with methotrexate. Infliximab was given by intravenous infusion in a dose of 3 mg per kg of the patient's weight at intervals of eight weeks (the first three doses are given 2 then 4 weeks apart, with subsequent doses given every 8 weeks). The infusions required the patient to attend a specialised outpatient infusion centre. It would have been known by the priority date that ACR50 improvement was seen in approximately 30% of patients on infliximab. Prof Edwards also stated that a rheumatologist would have known that the ACR20 response was approximately 60%, as reported in studies at the time, which I accept.

Etanercerpt

145. Etanercept is a fusion protein of a portion of a human soluble TNFα receptor and the Fc portion of a human antibody constant region. The human soluble TNFα receptor is a naturally occurring human protein which is used to deactivate TNFα. Therefore, etanercept functions as a "decoy" receptor, and thus is a TNFα inhibitor. Etanercept was licensed by the FDA for use in the treatment of RA in November 1998 and by the European Medicines Agency in February 2000.

146. Etanercerpt was seen as an improvement as it was licensed as monotherapy, and so could be administered to patients unable to tolerate methotrexate, and it was given as a fixed-dose 25mg injection twice a week, which meant that, unlike infliximab, etanercerpt could be self-administered by patients at home. By the priority date, it would have been known to the rheumatologist that approximately 40% of patients on etanercerpt were achieving an ACR50 improvement. Prof Edwards stated that he would have expected that the ACR20 improvements would also have been well known, being approximately 60-70%, which I accept.

D2E7

147. By the priority date, the skilled rheumatologist would have known that a fully human antibody against TNFα was in development and that it was known as D2E7. There was particular interest in D2E7 in light of the fact that it was a fully human anti-TNFα antibody.

Immunogenicity of biologic therapies

148. The human immune system can detect and react to "foreign" (non-human) proteins. Because they are proteins, biologic drugs can potentially trigger an immune response, which can lead to the patient's body recognising the drug as foreign and generating anti-drug antibodies ("ADAs"). An immunogenic response can lead to adverse events ranging from mild injection site reaction to anaphylaxis. The generation of ADAs can lead to a reduction of the therapeutic effectiveness of a biologic. By the 1990s, efforts were being made to create biologic agents with a higher proportion of human sequence (as opposed to the early murine monoclonal antibodies), in order to reduce immunogenicity. It was, however, known that the humanisation of a non-human antibody would not fully eliminate the risk of an immunogenic response.

The structure of clinical trials

149. Typically, clinical trials are designed and conducted in an iterative manner, where the results of the previous trials inform the design of subsequent trials. Traditionally, drug development has been categorised into four temporal phases: Phases I – III being pre-approval, and Phase IV being post-approval. The early studies will test a number of different regimens to assess safety and tolerance, and the later studies will focus primarily on efficacy. The Phases can be summarised as follows (although it should be noted that the prior art uses the "Phase" nomenclature in a different sense).

    i) Phase I: typically focusses on the pharmacokinetics of the drug, as well as preliminary dose ranging.

    ii) Phase II: the primary objectives are dose finding and checking for tolerability and side effects with a larger group. Preliminary indications of efficacy would also be looked for.

    iii) Phase III: The primary objective is to demonstrate or confirm therapeutic efficacy, also allowing assessment of tolerability and side effects in a larger population.

    iv) Phase IV: follows the drug post-approval to better identify and characterise its safety and real world effectiveness.

Approach to clinical trials and dosing regimens

150. The main factors the skilled team would consider are the following:

    i) Dose level. The skilled team would want to investigate a range of doses to ascertain the dose response relationship and to identify the window within which the drug was both safe and efficacious.

    ii) Dosing frequency. How often the drug should be administered.

    iii) Method of administration. Route of administration will be a consideration, particularly as biologics cannot be given orally.

    iv) Duration of treatment. The skilled team would consider the period of time over which administration was required. For TNFα inhibition, infliximab demonstrated that continuing treatment would likely be required.

    v) Adverse events. The skilled team would be mindful of potential adverse effects.

Background issues relating to pharmacology

Pharmacokinetics

151. The term "pharmacokinetics" describes the arm of pharmacology in which the absorption, distribution, metabolism and excretion ("ADME") of drugs is analysed to

ascertain the concentration of drug in the body. Concentration of drug may then be correlated with clinical response to determine appropriate dosing regimens. The pharmacologist will focus on blood plasma concentrations to draw observations on concentration of the drug in the blood stream and throughout the body.

Pharmacodynamics

152. Pharmacodynamics is the study of the body's response to a drug over time. The key parameter is the clinical response of the patient to a given concentration of drug (the measure of response will be determined before a study commences). As the dose of drug is increased, the clinical response usually increases, up to a point. This is known as a "dose response".

Linear kinetics

153. Linear kinetics is where the systemic drug exposure is directly proportionate to the dose given and the ADME of a drug is proportional to the amount of drug in the body. The systemic drug exposure is the total exposure that a patient has had to a drug at a given point in time. If the dose is doubled, the patient will be exposed to double the amount of drug. Professor Johnston states that for drugs with linear kinetics, provided the approximate values of the volume of distribution and the rate of clearance are known, plasma concentrations can be predicted with reasonable confidence. Professor Boddy is of the view that the pharmacokinetics must be fully categorised for this to be the case. I deal with this dispute later in the judgment.

Absorption, Distribution, Metabolism and Excretion

154. Absorption is the process by which a drug reaches the systemic circulation following extravascular administration. With intravenous administration, the administered dose is assumed to be absorbed fully in the plasma. If a drug is given by any other route (such as subcutaneous dosing) the rate and extent of absorption may vary, depending on factors such as drug solubility, blood flow at the site of absorption and the absorption site itself. The fraction of the administered dose that reaches the systemic circulation is referred to as the “bioavailability”. There is an issue between the parties as to whether any difference in bioavailability between intravenous and subcutaneous administration would affect the dosing regimen in relation to D2E7.

155. Distribution is the process by which the drug leaves and returns to the circulatory system and by which the drug is delivered to the tissues around the body. When a drug is administered to a patient, it is rarely distributed around the entire body. The "volume of distribution" is the apparent volume of the body that a drug is distributed in. Metabolism and excretion are the routes of drug “elimination”, a term which incorporates all of the processes involved in removing the drug from the body.

Compartmental models

156. Some drugs distribute quickly within the body, and the body can therefore be treated as a single container when assessing distribution. This is known as a “single compartment system” and is the most simple and frequently encountered pharmacokinetic model. Sometimes a drug can take longer to move in and out of

particular tissues (for instance, a drug may be bound by proteins in the tissues), and the body acts as a two (or more) compartment system. The compartments would have different rates of clearance and the drug would effectively have two half-lives.

Half-life

157. Drug clearance is the amount of the volume of distribution that is cleared of the drug, per unit of time. A half-life is the period of time it takes for the concentration of drug in a patient to fall by half. It is governed by the volume of distribution and how quickly the drug is cleared from the body. The half-life of a drug will depend on its chemical composition and the method of metabolism or excretion, and can range from minutes to weeks or even months.

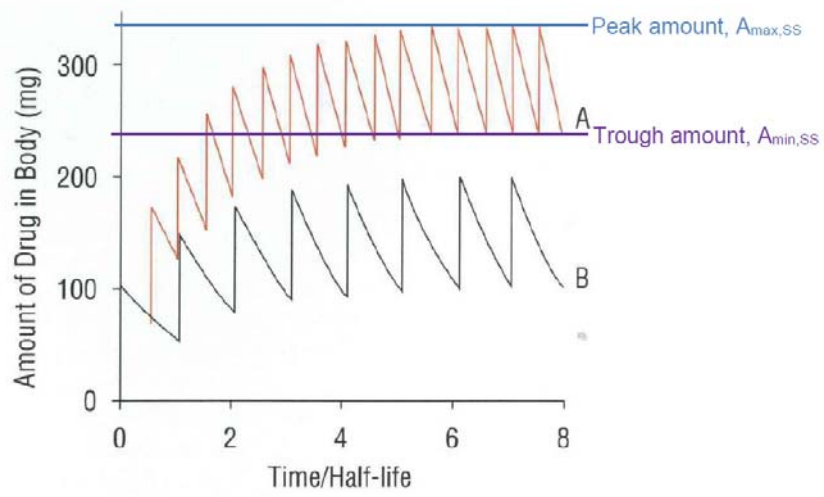
The t#herapeutic window

158. The therapeutic window is the range between the minimum effective dose and the maximum tolerated dose. The minimum effective dose is the lowest dose of a drug which causes a clinically relevant effect. The maximum tolerated dose is the dose just below the point at which unacceptable adverse events occur (caused by toxicity). The therapeutic window is thus the range in which the drug can be both safely and effectively administered. Administering a drug at the upper end of this range is wasteful as more drug is being administered than is required to produce the target therapeutic effect, which is both costly and unnecessarily risks side effect.

Repeat dosing: accumulation and the steady state

159. A dosing regimen does not require one dose to be completely cleared from the body before the next is administered, as doing so may (depending on the method of action of the drug) leave a time during which the patient is not receiving any (or adequate) therapeutic benefit. The effect of accumulation is shown in the following diagram, which was produced by Prof Johnston in figure 1 of his first report:

Figure 1. Dosing frequency controls the degree of drug accumulation. Curve A, i.v. bolus dose (100mg) administered twice every half-life; curve B, same bolus dose administered once every half-life. Note that time is expressed in half-life units.[10]



160. When subsequent doses are given regularly before the previous doses have been fully cleared, the concentration of the drug in the patient will accumulate over time to a point at which it varies between a consistent peak concentration (when doses are given), and a consistent trough concentration (the concentration to which the drug falls before the next dose is given). This is known as "steady state".

161. At steady state, the net amount of drug entering the body is effectively the same as the net amount of drug eliminated between doses. As shown in the diagram, the peaks and troughs in the amount of drug in the patient are initially variable, but after five half-lives, the peak and trough amounts become more constant, which is the time at which steady state is said to have been reached.

162. At steady state, the peaks and troughs are the maximum and minimum concentration or amount (depending on parameter measured). If a drug is administered once every half-life, at the steady state peak the drug will accumulate to double the amount of a single dose, and the trough at steady state will be equal to a single dose (half of the peak). If doses are administered more frequently than once per half-life, steady state will still be reached within five half-lives, but the peaks and troughs at steady state would be higher as there would be greater accumulation (see curve A in the figure above). If doses are administered less than once per half-life, the peaks and trough levels will be lower.

163. The aim in designing a dosing regimen would be to ensure that the concentration of drug in the blood is maintained above the level at which the target therapeutic response is lost, without reaching the maximum tolerated dose. The two main variables that can be adjusted to produce a dosing regimen are the dosing interval (frequency of administration of doses) and the dose.

The Common general knowledge in dispute

Legal Principles

164. I shall apply the summary of legal principles in respect of common general knowledge set out by Arnold J in *KCI Licensing v Smith & Nephew* [2010] EWHC 1487 (Pat); [2010] FSR 31 at [105] - [115], which was approved by the Court of Appeal; [2010] EWCA Civ 1260; [2011] FSR 8 at [6].

165. There was a debate between the parties as to whether the cited prior art should be looked at on its own (including the references cited therein) or in the light of further published references to D2E7 ("the Additional Prior Art"). The reason for this debate is because Prof Pope relied on the Additional Prior Art, which was found as a result of further searches by AbbVie's representatives.

166. The Claimants argue that as a matter of principle, the Additional Prior Art should not be considered. They point out that if a party, seeking to establish obviousness, were to rely on a mosaic of references not referred to in the prior art, that would clearly be impermissible (unless the mosaic was obvious, which is unusual). They assert that the correct starting point is the cited prior art read in the light of the common general knowledge. This may extend to documents cross-referenced in the cited prior art, but no wider (unless the other references are part of the common general knowledge).

167. I do not accept this proposition. There may be material which is not common general knowledge, which nonetheless, as a matter of routine, the skilled person would look for and find when approaching a particular problem. Amongst other cases, this is supported by the judgment of Arnold J in *KCI Licensing* at [112]:

> "It follows that, even if information is neither disclosed by a specific item of prior art nor common general knowledge, it may nevertheless be taken into account as part of a case of obviousness if it is proved that the skilled person faced with the problem to which the patent is addressed would acquire that information as a matter of routine. For example, if the problem is how to formulate a particular pharmaceutical substance for administration to patients, then it may be shown that the skilled formulator would as a matter of routine start by ascertaining certain physical and chemical properties of that substance (e.g. its aqueous solubility) from the literature or by routine testing. If so, it is legitimate to take that information into account when assessing the obviousness of a particular formulation. But that is because it is obvious for the skilled person to obtain the information, not because it is common general knowledge."

168. I consider that the skilled person interested in progressing a dosage regimen for D2E7 would look for and find the Additional Prior Art. Prof Edwards rightly accepted that this would be the case.

Areas of dispute in relation to common general knowledge

The aim of RA treatment

169. AbbVie relies on the fact that without effective treatment RA can be a profoundly disabling disease, causing great suffering and disability to patients and resulting in a significant healthcare burden, and that relapses can cause irreversible damage to the joints. Therefore, the aim of RA treatment in 2001 was to avoid the disease flaring, because that would lead to irreversible joint damage.

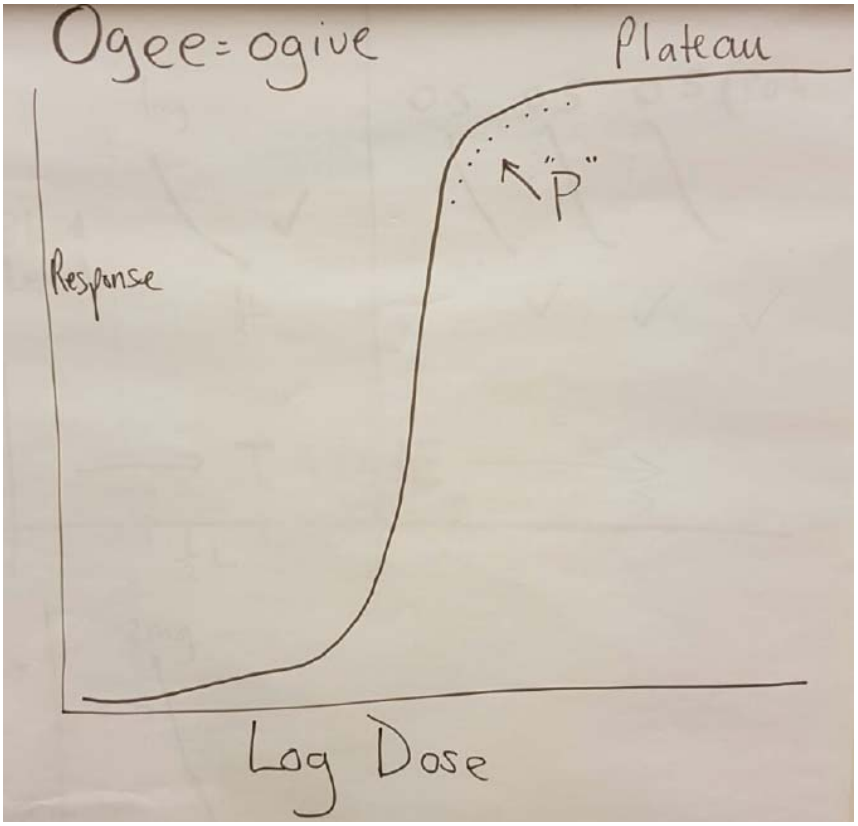
170. I agree that this would be the aim of an ideal treatment, but the skilled person would recognise that no one treatment will be beneficial to every patient. I have already referred to the evidence of Prof Johnston on this issue, which I accept. I also accept the evidence of Prof Edwards that when designing a dosage regimen for D2E7 the skilled person would be looking for a regimen which benefited the majority of patients, and could be adapted for a minority of patients. For example, as Prof Edwards explained, a dosage regimen of 40mg sc eow of D2E7 would be likely to suit the majority of patients of average weight, but it might need to be adjusted to a weekly regimen for heavier patients.

171. AbbVie further submits that Prof Edwards agreed that the aim was "to have complete control of inflammation all the time", and to give a therapeutic regimen that would, so far as possible, keep the disease in that state. A rheumatologist interested in developing a new RA treatment would have been aiming to achieve that outcome with the best ratio of benefit to risk in as high a proportion of patients as possible. I understood Prof Edwards to be saying that this was indeed the ideal outcome but in practice it would not be possible to achieve for all patients.

172. AbbVie submits that the aim of any regimen was to maintain the drug concentration at above the level needed to produce the target therapeutic response, and to administer the minimum amount of the drug capable of producing the maximum therapeutic response. I agree, with the caveat that this will never be possible for all patients, and so in practice the skilled person would seek to achieve this for as many patients as possible. Prof Johnston also made clear, and I accept, that as the skilled person would not want to overdose, he/she would start with a dose that would work effectively for the majority of patients.

173. Prof Edwards' evidence, which I accept, was consistent with this. He explained that the skilled team would want to investigate a range of doses to ascertain the dose response relationship and to identify the window within which the drug was both safe and efficacious. He illustrated this with a simple diagram during his cross-examination. The target would have been to investigate a range of doses at or near "Point P" on the dose response Ogee.

Curve (X/4)



174. The point "P" is just at the top of the steep section of the dose-response curve where it begins to flatten out to a plateau. Prof Edwards explained this at 3/255/18 – 256/2:

> "There is a point P here I have drawn of interest, which I call the point of plateau, or the onset of plateau, which is not a point, as you can see. It is a curve. One has to make a pragmatic decision as to whether you go for right up on to the plateau, which is a bit expensive and potentially toxic, or you take somewhere about here and, if you do that, you may want to think that most of the patients will get a good result, but you might want to increase the dose for a proportion of patients …"

175. So Point P was an appropriate starting point, although the skilled addressee designing a definitive study would do further tests above and below that dose level. Furthermore, Prof Edwards explained at 3/273/15:

> ".....Of course, point P …is an area and if you are a little bit low on point P, you still would be expecting to get a substantial number of patients well and have a good therapeutic effect. You would have the standard option that we have in rheumatology of giving a double dose or a one and a half dose

> to some patients if you thought they were getting suboptimal responses"

Patient weight and other sources of variation

176. AbbVie points out that patients will vary in a number of characteristics, including weight, where the average is 72kg but there are considerable variations around the average, pharmacokinetic parameters (for example clearance, volume of distribution and half-life) and pharmacodynamic parameters.

177. AbbVie submits that the therapeutic aim (which is a matter for the clinician) would be to obtain the desired therapeutic effect in as many patients as possible. This, AbbVie argues, requires that an increased dose be used, as compared to that for the average patient, although the magnitude of any necessary increase will be unknown without access to the underlying data on variability.

178. I do not accept this approach, for reasons which I have already indicated. Prof Edwards explained the average weight approach very clearly at [21] of his reply evidence, which I accept:

> "The Rheumatologist would of course be conscious that patients at the extremes of the size spectrum might need a modified dose (although this is an issue of volume of distribution, not clearance). However, most adult RA patients fall within a reasonably narrow lean body mass range, which means fixed dosing is a practical option. Moreover, the Rheumatologist would be aware that fixed dosing was used without problems with many drugs and experience with etanercept had confirmed that this was likely to be practical for TNF inhibitors."

179. Furthermore, I do not accept Prof Boddy's evidence that the prior art contains too little information for the pharmacologist to proceed, or that an increased dose is required to be used as compared with that for the average patient. I accept Prof Johnston's and Prof Edwards' evidence that the pharmacologist, for a drug with a wide therapeutic window, would start at the lowest dose that would be likely to benefit the majority of patients, and adjust, for example from a two week regimen to a one week or one-and-a-half week regimen for heavier patients. Prof Edwards made clear during his cross-examination, and I agree, that it would not make sense to dose to the maximum for all patients, and thereby to overdose the majority.

The significance of ACR20 results

180. As to the significance of ACR 20 results, at [3.16] of her first report, Prof Pope stated that:

> "ACR20 was recognised at the Priority Date as a minimum threshold for distinguishing active drug from placebo. However, for an RA patient with moderate to severe disease, achieving no more than an ACR20 would represent a minimal

> clinical improvement. It would not have been a clinical target for a rheumatologist (or a patient) at the Priority Date."

181. Prof Edwards disagreed with this at [7] of his second report. He said:

> "…the ACR20 grade is not a minimal improvement. As explained in my First Report at paragraph 41, although ACR20 sounds modest, it represents a significant improvement for patients, especially for those patients with moderate to severe RA who may have failed to respond to a number of DMARDs. To obtain ACR20 requires complete reversal of swelling and tenderness in at least some joints. The ACR50 and ACR70 response rates have a significant disadvantage in early studies because the numbers of patients achieving those responses are relatively small and therefore likely to be subject to more variation from trial to trial. Since the rates for ACR20, ACR50 and ACR70 tend to follow similar relations when considered across drugs in the same class the ACR20 rate is a practical primary outcome measure. In 2001, ACR20 was generally regarded as the primary efficacy measure on the ACR scale for trials of new drugs."

182. Both of the experts maintained their position during cross-examination. I have no doubt that Prof Edwards was correct about this. When the ACR Committee set out to develop a uniform standard for RA clinical trial measurements they surveyed rheumatologists to establish what was commonly regarded as a meaningful improvement among patients. The survey showed that if the tender or swollen joint count improved by 20%, or other outcomes improved by more than this, the clinician would consider this to be a relevant improvement. This was published by Felson et al., in Arthritis & Rheumatism (*Arthritis Rheum*, 1998, 41(9), 1564-1570). The survey concluded that:

> "..... ACR20 should continue to be the primary measure of efficacy in RA trials, with higher thresholds for improvement being determined and reported as secondary efficacy measures."

183. This explains why leading rheumatologists reported ACR20 results in renowned journals. For example, Weinblatt et al. relied on such results in their seminal paper concerning etanercept in N Eng J Med. 1999, 340(4), 253-259. Maini et al. also relied on ACR 20 results in their paper concerning infliximab published in the Lancet (*Lancet*, 1999, 354, 1932-1939).

184. There was some debate about the meaning of "primary measure of efficacy" also known as "primary variable" or "primary outcome". This is made clear in the FDA's E9 Guidelines, published in 1998 as *"Guidance for Industry: E9 Statistical Principles for Clinical trials"*:

> "There should be sufficient evidence that the primary variable can provide a valid and reliable measure of some clinically relevant and important treatment benefit in the patient population described by the inclusion and exclusion criteria"

185. The reference to "some clinically relevant and important treatment benefit" is inconsistent with Prof Pope's evidence that ACR20 represents "a minimal clinical improvement."

186. Prof Edwards explained that ACR20 was the standard measure of clinical efficacy and that ACR50s and ACR70s were useful to have, but secondary. This was because such results could indicate a substantial improvement in a patient's quality of life. It is wrong to think of ACR20 as an indication that a patient only gets 20% better, as it includes all patients who achieve an improvement of up to 49% and all patients who would also achieve ACR50 and ACR70. Prof Edwards made it clear at 2/122-3 that the rheumatologist would love to have seen a complete remission of all disease activity. But this would not be possible in many patients. He said:

> "A considerable portion of these patients, even if you gave them the very best drug you could get your hands on, would only achieve ACR50. Some of them might only achieve ACR20 because, in reality, they had achieved ACR49 and you are not allowed to have anything except ACR20 and ACR50. I do not think that the implication here is at all that an ACR20 or 50 improvement is not something that the patient might be extremely grateful for."

187. I accept that a clinician prescribing a drug for RA would like to see as many patients as possible achieving an ACR50 or ACR70 response, but it is quite clear that ACR20 is a significant improvement, which was in use long before the priority date as the primary measure of efficacy for studies in support of clinical trials. This case is concerned with early clinical trials on patients with RA, and what, if any, were the obvious ways of progressing a dosage regimen for D2E7. ACR 20 results are highly relevant to that question.

188. Prof Pope's answers during cross-examination suggest that she was approaching the question from the perspective of a prescribing physician rather than a skilled person interested in routine developments from the prior art for a dosage regimen for D2E7. For example at 5/632 she said in relation to ACR20:

> "So that is where I think the difference is. It is a very relevant end point. Is it the most clinically relevant to me or to treating physicians? No."

189. Prof Pope also suggested that the rheumatologist would have been looking to achieve at least as good results in clinical trials for a new biologic therapy as those achieved with infliximab and etanercept. At [3.17] of her first report she said, in relation to these therapies, that:

> "Patients on the key clinical trials of these therapies were achieving ACR50 responses in around 20-40% of patients after around six months. The better non-biologic therapies available were known to produce ACR50 responses in around 30% of patients (see for example studies comparing the then new DMARD leflunomide with sulfasalazine and methotrexate, where ACR50 responses were seen in between 22% to 34% patients on each of these DMARDs in various different studies). The Skilled Clinician would therefore be looking to achieve at least as good results in clinical trials for a new biologic therapy."

190. Mr Tappin clarified in closing that there was no suggestion that D2E7 would not be taken forward because it did not report such ACR50 data, but rather that the absence of such data was relevant to considering the dosage regimen to take forward, given that the rheumatologist is trying to achieve a higher level of clinical response than ACR20s.

191. I do not accept this. Prof Edwards explained that ACR50 and 70 data can only be used where the study is large enough to have the necessary statistical power. So the skilled person would certainly not wait around for ACR50 and 70 data before progressing a dosage regimen for D2E7, or attach less value to the primary outcome ACR20 results.

192. Furthermore, Prof Edwards' evidence, based on his extensive experience, was that ACR20 data could, as a rule of thumb, be used to predict what the ACR50 and 70 data (if available) would be likely to look like, because there was "a pretty constant pattern" of the relationship between them. It is strongly disputed by AbbVie that this was common general knowledge, even though it may have been Prof Edwards' experience. It points out that he was unable to point to any document which recorded this.

193. Prof Edwards' evidence seemed to me logical and convincing as a broad proposition. Not all basic knowledge has to be written down. I accept his evidence that this was the kind of thing that everyone knew but nobody mentioned. In fact, the trend can be seen from the tables at X/9. The data for infliximab was published by Maini et al. in the Lancet (*Lancet*, 1999, 354, 1932-1939), and shows the relationship which Prof Edwards indicated was well known. However, my decision would be the same irrespective of this relationship, since it is accepted that the absence of ACR50 results would not deter the skilled person from taking forward D2E7.

The convenience of fixed-dose subcutaneous administration

194. At [113] of his first report, Prof Edwards said:

> "The Rheumatologist's preference would have been to administer D2E7 in fixed doses (a fixed mg amount), rather than variable (mg/kg) dosing, because it is much easier and cheaper to prepare and distribute fixed s.c. doses, rather than preparing syringes with variable doses on a patient-by-patient

> basis. Individually tailored dosing is more prevalent in early drug development when solutions are made up on site and administered i.v., or if there are toxicity concerns which require the administration of only the exact amount of drug required. As D2E7 has a wide therapeutic window, a fixed dose could be used (as was the case with etanercept)."

195. Prof Pope disputed this at [7.1] of her second report. She said:

> "At Paragraph 113(b) Professor Edwards states that "the Rheumatologist's preference would have been to administer D2E7 in fixed doses (a fixed mg amount), rather than variable (mg/kg) dosing, because it is much easier and cheaper to prepare and distribute fixed s.c. doses, rather than preparing syringes with variable doses on a patient-by-patient basis". I do not agree with this statement. The Skilled Clinician's preference would be to find an effective and safe dosing regimen that produces the best ratio of benefit to risk in as high a proportion of patients as possible (as I state at Paragraph 3.56 of my First Report). Professor Edwards describes essentially the same approach at the beginning of Paragraph 113: "the Rheumatologist would have wanted to administer the minimum amount of drug capable of producing the maximum therapeutic effect". This overarching aim of the Skilled Clinician would be the only consideration as to whether the ultimate regimen involved fixed doses or variable/weight-based doses; issues such as cost and convenience would not be relevant to the Skilled Clinician at this stage of the clinical trials."

196. I have no doubt that Prof Edwards is correct about this. The convenience to the patient of being able to self-administer fixed doses of a drug at home, rather than being required to visit a hospital, are obvious. The cost advantages are also clear. I understand Prof Pope's view that some patients prefer to attend hospital for i.v. infusions so that they can "get their social time with nurses", but for most patients, as Prof Edwards indicated, hospital visits are, if possible, to be avoided.

197. During cross-examination Prof Pope accepted that in general, she preferred her patients to be on subcutaneous doses because it cost the system less; 562/3-5. The same is obviously true of fixed doses, as opposed to personalised doses for individual patients, as Prof Edwards explained. Prof Pope suggested that issues such as cost and convenience would be irrelevant to the skilled person at this stage of the clinical trials. I do not accept this evidence. The prior art is considering development of a dosage regimen for D2E7. If a dosage regimen is not considered at this stage, then it will not be pursued, and will not gain regulatory approval.

198. The advantages of fixed-dose subcutaneous administration of etanercept were already clear. There would be a strong motivation to achieve the same advantages for any competing drug.

The development of anakinra

199. Prof Pope's first report listed various trials of biologics for the treatment of RA in which she had been involved; [1.16]. She omitted to mention her work on the IL1 drug inhibitor, anakinra. I consider that this work was relevant, because anakinra is a biologic which was developed close to the priority date to treat RA. It was, and is, administered as a fixed-dose subcutaneous injection. Furthermore, it was included in a comparative study with etanercept, D2E7 and infliximab, which was published by Cohen et al. in Arthritis & Rheumatism (*Arthritis Rheum.*, 2002, 46(3), 614-624). So it was clearly relevant to the subject matter of these proceedings.

200. The authors of Cohen et al. included Weinblatt, Moreland and others, and Prof Pope described many of the authors as "very big names". The study tested anakinra in combination with methotrexate. The abstract explains that the primary efficacy end point was the proportion of subjects who met the American College of Rheumatology 20% improvement criteria (attained an ACR20 response) at week 12. After considering the ACR20 responses, the authors were prepared to conclude that:

> "In patients with persistently active RA, the combination of anakinra and MTX was safe and well tolerated and provided significantly greater clinical benefit than MTX alone."

201. Prof Pope made no suggestion that she was unaware of the Cohen paper. On the contrary, it was published by leaders in the field and concerned a drug on which she had worked. In the light of her evidence in paragraph [3.16] of her first report concerning ACR 20 responses, she should have referred to anakinra and explained why she was able, nonetheless to give this evidence.

202. Furthermore, the "Treatment" section on page 2 of Cohen et al. explained that, in addition to MTX, patients were given either placebo or anakinra "administered as a single, subcutaneous injection." Given Prof Pope's strong preference for i.v. infusions as opposed to subcutaneous injections, this should, again, have been referred to and explained.

203. Page 7 of Cohen et al reported percentages of patients achieving ACR20, ACR50 and ACR70 responses at weeks 12 and 24. Cohen et al report that 19% of patients treated with anakinra 1.0 mg/kg and 24% of those treated with anakinra 2.0 mg/kg achieved an ACR50 response. The equivalent figures for ACR70 responses were 5% and 11%. I have referred to Prof Pope's evidence that the skilled clinician would be looking to achieve at least as good results in clinical trials for a new biologic therapy as had been reported for infliximab and etanercept. These results were not nearly as good, and yet Cohen et al were enthusiastic in their conclusions about anakinra. They stated that:

> "The results of this trial demonstrate that the combination of anakinra and MTX offers a new alternative for patients with ongoing active disease despite MTX therapy. Long-term follow-up and evaluation of the effects of this combination on retarding radiographic progression will determine the place for this therapy in the treatment area for patients with RA"

204. This is inconsistent with Prof Pope's evidence, and, had her criteria of "at least as good ACR50 and ACR70 results as infliximab and etanercept" been applied, then work on anakinra would have stopped. In fact, it proceeded to obtain marketing authorisation, and is still on the market. When asked about this issue at 567/15-568/13 she twice stated that she did not know what the question was. In my view, the question was clear, and there was no answer to it.

205. When asked why she had excluded anakinra from the list of biologic trials for RA, as set out in her report, Prof Pope stated at 4/558/23:

> "Yes, it could have been in but I do not think there is any significance to me at least, having it in there or not. I am not trying to [be] extensive as you already have my CV. It is just highlighting some of the clinical trials."

206. I was not satisfied with this explanation, although I accept that the omission was inadvertent. The development of anakinra was not consistent with significant parts of her evidence, and was highly material.

Half-life and the rule of thumb

207. This is relevant to dosing frequency i.e. how often the drug should be administered. It was common ground between the experts that repeatedly dosing a drug at intervals at which the drug remains in the body from the previous dose will lead to accumulation. Profs Edwards and Johnston explained in their first reports that, as a "rule of thumb' repeat dosing every half-life was a good starting point, because the drug accumulates in the body. Prof Edwards said at [113(a)] of his first report that:

> "In 2001, and still now, it was generally understood that with repeated dosing once a half-life, this accumulation will mean that each dose is effectively equivalent to double a single dose (i.e. 0.5 mg/kg every half-life would accumulate to be equivalent to a single dose of 1mg/kg)."

208. AbbVie disputes the existence of such a rule of thumb, suggesting that there was no evidence for it. I disagree. In her report to the Canadian Patent Appeal Board Prof Pope said that "Although half-life can give a feel for potential dosing interval, it alone can never determine the interval". This appears to be another way of expressing the "rule of thumb" concept and Prof Boddy readily agreed. Prof Pope stated in her written evidence and during her cross-examination at 5/655-6 that she could not comment on this issue as a skilled clinician. I did not find this satisfactory, as she had chosen to comment on the same issue in the Canadian proceedings.

209. At 5/645 she suggested that the issue was very complicated and she would need the help of a skilled pharmacologist. When asked why half-lives were included in the Physician's Desk Reference (Canadian Legal Compendium), a standard text for clinicians, she suggested that this was only for toxicology incidents following an overdose. I do not accept that this is the sole reason for inclusion, nor do I accept that

the concept expressed by Prof Edwards was a complex one. I believe that it would have been well known to the skilled rhematologist at the priority date.

The Kempeni papers

The status of the Kempeni papers

210. AbbVie submits that the Kempeni papers would not have been peer reviewed and reported preliminary data which would have been treated with caution. In my view, this fails to have regard to the nature of the papers, both in terms of their authors and their audience. The papers were presented by world-leading rheumatologists to conferences at which other leaders in the field were invited; XX Pope 5/614-5. Their contents would have been taken extremely seriously, and very carefully considered.

Kempeni 1999: "Preliminary results of early clinical trials with the fully human anti-TNFα monoclonal antibody D2E7"

211. Kempeni 1999 begins by considering the state of the art in relation to the treatment of RA and states that:

> "The more promising of [innovative] treatments seem to be those that block the effects of tumour necrosis factor (TNF)α because this proinflammatory cytokine seems to play a central part in the immunopathogenesis of RA."

212. It explains that infliximab, etanercept and another potential anti-TNF*α* biologic agent, CDP571, contain non-human elements and can be immunogenic, whereas D2E7 is fully human and "may have low immunogenicity" and "greater therapeutic potential". Prof Edwards points out, and I agree, that these features of D2E7 would have made the rheumatologist think it was highly worthwhile for D2E7 to be taken forward in the clinic.

213. Kempeni 1999 then reports the outcome of four phase I trials with D2E7.

(i) Single dose, dose escalating study (DE001)

214. Kempeni 1999 refers to a clinical trial known as DE001, which is described further in the abstract van de Putte 1998. This was a double-blind placebo-controlled single-dose clinical trial. In the DE001 study, 120 patients (in 5 groups of 24) were treated with doses of D2E7. Groups of 24 patients (of which 18 received drug and 6 received placebo) were studied with, in ascending order, intravenous single doses of 0.5, 1, 3, 5 and 10 mg/kg adalimumab (referred to as D2E7). Prof Edwards explained, and I accept, that in early trials, i.v. infusion is often useful for safety reasons, because infusions can be stopped if adverse reactions occur, and infusion ensures all of the drug enters the bloodstream.

215. Kempeni explains that the purpose of this study was to determine the pharmacokinetics of D2E7 and evaluate safety and efficacy in terms of onset, duration and magnitude of response. It states that:

> "Treatment was tolerated very well. No clinically relevant and dose related adverse drug reactions were observed. The therapeutic effects became evident within 24 hours after study drug administration and peaked at week 1-2. 19, 41, 72, 67, 56, 78% of the patients achieved response status at any time after treatment with placebo or 0.5, 1, 3, 5, 10 mg/kg D2E7. Response on day 29 after dosing was 0,6, 28, 33, 44, 39% respectively. Some responses were observed up to week 12."

216. Kempeni 1999 describes the results as follows:

> "The data from this first therapeutic trial in humans were very encouraging. In the three highest dose groups, 40-70% of patients achieved DAS and ACR20 response status at 24 hours to 29 days of treatment. The therapeutic effects became evident within 24 hours to one week after D2E7 administration and reached the maximum effect after 1-2 weeks, with dose response reaching a plateau at 1 mg/kg D2E7. In contrast, only 19% of patients taking placebo achieved response status. Single doses of D2E7 were well tolerated and the dose increment scheme was followed as planned reaching the maximum dose of 10 mg/kg without any evidence of clinically relevant or dose related adverse effects."

217. Prof Edwards attached importance to the statement that "the therapeutic effects… reached the maximum effect after 1-2 weeks, with a dose response reaching a plateau at 1mg/kg". He explained that the fact that the dose response plateaus at 1 mg/kg indicates that giving more than 1 mg/kg has little additional therapeutic benefit. In other words, it is the point "P" on his dosage response curve illustrated above. His view is that the skilled rheumatologist would have considered it promising that the dose response plateau occurred at a relatively low dose, as this meant that a relatively small amount of D2E7 would be needed to elicit the full clinical response. I accept his evidence.

218. The description of the DE001 trial in Kempeni 1999 is, in my judgment, supported by a consideration of the disclosure of Van De Putte 1998, which is unsurprising, given that Kempeni had access to it and was reporting on its results. In particular that abstract reports on the proportion of patients achieving the relevant DAS response in each arm, namely 19% for placebo, and 41%, 72%, 67%, 56% and 78% for the increasing treatment arms. So the relevant proportion at 1 mg/kg was 72%, and had plateaued. These would have been understood to be the data to which Kempeni 1999 was referring when it said that the "dose response reach[ed] a plateau at 1 mg/kg D2E7."

219. AbbVie advances numerous criticisms of Prof Edward's evidence in this respect. It alleges that he ignored the nature of the plateau referred to in Kempeni 1999, which means no more than that the patient has achieved a DAS improvement of about 1.2 at some point. This, it is said, tells the skilled reader nothing about the magnitude of the response obtained in each of the different treatment groups, nor about the duration of

the response. It does not distinguish between a markedly good DAS response sustained over a long period, and one in which a patient scraped over the 1.2 improvement threshold for a couple of days.

220. Whilst this is supported by the evidence of Profs Pope and Boddy, I do not accept that it undermines the validity or significance of the data given in Kempeni 1999 and Van de Putte 1998. Plainly, the authors of those documents, who were well qualified to judge, considered that this improvement in DAS score was relevant and significant, which is why they chose to report it. Furthermore, the significance of the information concerning the plateau of the effectiveness of the dose response curve would have been apparent to the skilled person. The FDA E9 Guidelines, current at the time, support the view that for a drug which has a wide therapeutic window (such as D2E7) the starting dose should be on or near the plateau of effectiveness of the dose response curve:

> "Use of Dose Response Information in Choosing Doses
>
> What is most helpful in choosing the starting dose for a drug is knowing the shape and location of the population (group) average dose-response curve for both desirable and undesirable effects. Selection of dose is best based on that information, together with a judgment about the relative importance of desirable and undesirable effects. For example, a relatively high starting dose (on or near the plateau of the effectiveness dose-response curve) might be recommended for a drug with a large demonstrated separation between its useful and undesirable ranges."

221. AbbVie also alleges that the dose response data in van de Putte 1998 at day 29 was provided, by which time the response for the 1.0 mg/kg doses was disappointing; and that as regards efficacy in terms of patients who achieved both ACR20 and DAS, only the three highest groups achieved 40-70% response rates. I have had due regard to these points, but, again, I do not accept that they undermine the validity or significance of the data given in Kempeni 1999 concerning the plateau. All of this information is referred to in Kempeni 1999 and I see no reason to question the author's conclusions. Indeed, both Kempeni 1999 and van de Putte 1998 are extremely optimistic in their conclusions, and do not suggest any disappointment in the 1 mg/kg dose results.

222. Pharmacokinetic information was also reported in DE001. Van de Putte 1998 says that a preliminary analysis revealed a half-life of about 10 days. Kempeni 1999 discloses more precise half-life figures and says the following:

> "Pharmacokinetic parameters were calculated for a total of 89 patients from all dose groups. The systemic drug exposure (AUC) increased proportionally with increased dose. The mean total serum clearance was 0.180 to 0.271 ml/min, and the steady state volume of distribution ranged from 0.063 to 0.076 l/kg indicating that distribution of D2E7 was mostly in the

> intravascular space. The estimated mean terminal half life was 11.6 to 13.7 days."

223. Prof Edwards' view is that the skilled rheumatologist would have been interested in the half-life of D2E7 (estimated at 11.6 - 13.7 days) as it gives an indication of how long the therapeutic effect might last. Prof Pope considers that that would be a matter for the pharmacologist, and so did not contradict Prof Edwards.

224. Prof Johnston analysed the pharmacokinetic information in Kempeni 1999 as follows:

i) *Systemic drug exposure (AUC): increased proportionally with dose.* This tells the pharmacologist that as the dose is increased, the amount of drug in the body increases proportionally (i.e. the drug has linear kinetics). This enables the pharmacologist to predict (within the tested range) what dose is required to produce a particular amount or concentration of drug in the body.

ii) *Volume of distribution: 0.063 – 0.076 l/kg***.** Kempeni reports that the data suggest the drug was mostly confined to the intravascular space (the blood). This indicates to the pharmacologist that D2E7 has simple pharmacokinetics and that it can be treated as a one compartment system.

iii) *Clearance: 0.180 – 0.271 ml/min.* The range reported is not particularly large and the values are low, indicating that D2E7 is cleared relatively slowly from the body.

iv) *Half-life: 11.6 – 13.7 days.* The half-life is given as a range.

225. His opinion was that since the ranges are relatively narrow the Pharmacologist would work on the basis of the value in the middle of these ranges – i.e. volume of distribution 0.070l/kg; clearance 0.225ml/min; and half-life 12.7 days.

226. Most of this was common ground between the pharmacologists. The dispute concerned whether Prof Johnston was correct in concluding that D2E7 has simple pharmacokinetics and can be treated as a one compartment system. Prof Boddy's view was that this could not be assumed from the information that distribution of D2E7 was mostly in the intravascular space. He disagreed that this indicated that a one-compartment model would describe the pharmacokinetics. He explained that because the volume of plasma is about 3L, whereas the volume of distribution given in Kempeni 1999 is 5L (for a 72kg patient), about half to a third of the drug is outside the plasma and may be distributed to another pharmacokinetic compartment.

227. Prof Boddy's view was that the pharmacologist could not assume that the remaining drug was within the red blood cells. Alternatively, even if he could, he could not assume that drug within the red blood cells would not form a second pharmacokinetic compartment. Prof Johnston strongly disagreed with this assessment. I accept the evidence of Prof Johnston on this issue, for the following reasons:

228. First Prof Johnston explained, convincingly, that a one-compartment model was appropriate for the Kempeni data – because if the drug was not in the plasma then it was in the blood. He said at 3/386-7:

> "With distribution, what you typically see with a one-compartment system is that you have tissues that are highly perfused and with red blood cells they are not even perfused. They are sitting in the plasma so they are actually there. I would not expect it to act as a compartment. I know of no drug where the red cells act as a compartment. The fact that we have a five litre volume of distribution to me says that the drug is in blood."

229. Secondly, Prof Boddy's concern arose because he understood the available volume of plasma (ca. 3 litres) to be significantly less than the volume of distribution of D2E7 (ca. 5 litres). There is no indication of this concern in Kempeni 1999. Prof Boddy acknowledged that where multi-compartment pharmacokinetics exist, it is normal to report this. However, he asserted that Kempeni did not address the issue of multi-compartment models because his audience might not be interested in the issue. This seems most unlikely, as Kempeni contains express references to pharmacokinetic data.

230. Thirdly, Prof Boddy's theory, which would require extravascular distribution of adalimumab, would, if correct, be most unusual. The 1995 edition of the standard textbook Rowland and Tozer (Rowland M. and Tozer T. N., *Clinical Pharmacokinetics: concepts and applications*. 3rd ed. USA: Lippincott Williams & Wilkins, 1995), refers to extravascular distribution of biologic drugs being "very slow to non-existent".

231. Fourthly, the 2006 edition of another text by Rowland and Tozer (Tozer T. N. and Rowland M., *Introduction to Pharmacokinetics and Pharmacodynamics: the quantitative basis of drug therapy*. 1st ed. USA: Lippincott Williams & Wilkins, 2006), gives adalimumab as the textbook example of a drug confined to the plasma (based on its volume of distribution of 5-6L) (p. 89). I bear in mind that this text post-dated the priority date. However, it is inconsistent with Prof Boddy's theory, and he did not agree with the textbook. This suggests that his theory would not be shared by the notional person skilled in the art.

(ii) Multiple ascending dose study (DE003)

232. Kempeni 1999 reports a further study (DE003), which is described further in Rau 1998. Once the response to the single dose had worn off (and after a minimum of 4 weeks), patients entered a multiple dose, open label extension study. Initially, D2E7 was administered every two weeks (i.v.) until patients obtained a "good" response (absolute DAS < 2.4). Then, "to measure the duration of the good response, patients were re-treated only upon disease flare up." Prof Edwards expressed the view that the rheumatologist would consider it reasonable for the extension to be open label as the study was focused on pharmacology, rather than the presence or absence of a response.

233. On reading Kempeni 1999, Prof Edwards' view was that the rheumatologist would have thought that a two week dosing interval had primarily been selected on the basis of the findings that the half-life of D2E7 was around two weeks (11.6 - 13.7 days).

The rheumatologist would have considered a dosing interval of a half-life to be a good starting point.

234. Patients received the same doses as in the single dose study, but patients who did not respond well with 0.5 or 1 mg/kg were offered 3 mg/kg. Kempeni does not say whether increased doses were taken and, if so, whether they improved the response in patients with inadequate responses (i.e. those patients may have been totally unresponsive to D2E7).

235. The results of this study were: Re-treating patients only on disease flare-up led to more than 80% achieving DAS of 1.2 or more, and a mean dosing interval of 2.5 weeks was observed. Prof Edwards considered that this response rate is high and the rheumatologist would have been encouraged by the results. He further considered that the mean dosing interval of 2.5 weeks implies that once patients had achieved a "good" response, they began to experience symptoms again after an average of 2.5 weeks.

236. Kempeni 1999 summarises the results of the DE003 trial as follows:

> "Response rates of more than 80% have been achieved with a mean dosing interval of 2.5 weeks. After six months, 86% of patients continued to receive treatment with D2E7 indicating that long term intravenous treatment with D2E7 in the dose range from 0.5 to 10 mg/kg was well tolerated."

237. Prof Edwards also noted that Rau 1998 states that in the DE003 open label extension study, more than 1400 doses of D2E7 had been given for up to 12 months and only 12 of the 120 patients had dropped out (6 due to lack of efficacy and 6 due to other ailments). The reported reduction in SWJC and TJC (around 60%) appeared to continue for at least 12 months. He considered that this demonstrates a sustained response with D2E7 and the rheumatologist reading this would have expected D2E7 to be suitable for use as a long-term therapy.

238. AbbVie heavily criticised the reliance by Profs Edwards and Johnston upon the 2.5 week dosing interval in DE003 as supporting their view that a two week interval would produce a good response, for the following reasons:

239. First, the reporting of the DE003 trial does not differentiate between the dosage groups, with the effect that the skilled reader cannot determine the proportion of patients in each group who achieved responder status, nor what percentage in each group achieved a 'good' response, nor the magnitude or duration of the responses in each group. Prof Edwards agreed with this.

240. Secondly, in relation to the 2.5 week dosing interval, AbbVie argued that since redosing was triggered by the loss of a good status, i.e. disease flare, and was only on average every 2.5 weeks, that indicated that a large proportion of patients needed treating at least every 2 weeks because the disease had flared, and hence would need treating more frequently than every 2 weeks to avoid losing control of the disease. It relies on the cross-examination of Prof Edwards at 2/240/14-241/5:

> "A.I would agree that it suggests that two weeks is on the threshold of what you would need. I think it is very difficult to interpret precisely beyond that.
>
> Q.If you have a large proportion of patients requiring dosing at two weeks because their disease has flared, that suggests you should be dosing them more frequently otherwise you lose control of the disease which, as we discussed earlier, is what you want to avoid.
>
> A.I think -- no, I agree that it would tend to point that one might think in that direction, yes."

241. Thirdly, Kempeni 1999 and Rau 1998 do not give information about the dosing interval in different dosing groups. Prof Edwards would have expected a shorter interval for the lower doses, as one would expect a shorter response time with a lower dose.

242. Fourthly, once cannot tell from the reports of DE003 what proportion of patients on the 0.5 mg/kg regimen achieved a good response after two weeks. Prof Edwards accepted that DE003 did not give any further information about whether this dose would be good after two weeks.

243. Finally, AbbVie submits that overall, Prof. Edwards' view was that no information about dose responses could be obtained from DE003, and that all of the response data came from the results of the DE001 study. Therefore it is said that the skilled person would not take forward a regimen of 0.5 mg/kg on a two weekly basis. It relies in particular on the cross-examination of Prof Edwards at 2/249/13-18:

> "Q. Looking at this all in the round, professor, surely you would agree that there is nothing here to indicate that 0.5 mg per kg as a repeated two weekly regimen is efficacious?
>
> A. I would not attempt to draw that information from DE003 at all, no, because we do not have any dose-related information from DE003"

244. When assessing this overall submission, it is necessary to continue to read the cross-examination of Prof Edwards, which proceeded as follows:

> Q. Professor, I would suggest that the skilled person looking at this information that we have looked at so far in these papers would conclude that you would not take 0.5 mg per kg every other week forward on an IV basis, you should use doses no lower than 1 mg per kg.
>
> A. I do not follow the -- my feeling is that DE003 does not tell us anything about that. In terms of dose-ranging, we are relying on DE001, the initial study, and we have two sets of dose response data which suggests that -- doing the calculations that we have discussed, that 0.5 mg per kg given every half-life would be just at the bottom or

> is likely to be just at the bottom of the dose response curve, we cannot be sure about that, but it is likely to be about that area."

245. My conclusion is that DE003 was not intended to provide dose response information, and does not do so. A non placebo controlled, open label study could not be relied on for that purpose. Of itself, it does not provide sufficient information to take forward 0.5 mg/kg every other week, either on an i.v. or subcutaneous basis, and that is not its purpose. However, Kempeni 1999 does not consider DE003 in isolation. Rather, it considers it in combination with the other trials that it reports, including DE001. I consider that the skilled person would draw the following, limited, conclusions from DE003:

246. First, the skilled person would understand that a two weekly dosing interval was used in the initial part of the DE003 study because this is roughly equal to the reported half-life of D2E7, and the half-life is often used as a starting point in informing the choice of dosing interval. As stated above, the half-life of D2E7 is reported by Kempeni 1999 to be on average 12.7 days. In practice, it would not be sensible to administer the drug once every 12.7 days, so the dosing interval would be rounded up to two weeks for convenience, as appears to have been done in this study.

247. Secondly, after reaching a "good" status, patients were re-dosed only when symptoms flared up which, on average, was after two and a half weeks (i.e. loss of response occurred after an average of two and a half weeks). This provides some indication to the skilled person of the limit of the dosing interval with the doses tested, which lends some further support to a dosing interval of two weeks, when Kempeni 1999 is read as a whole, including Kempeni 1999's description of DE001.

248. Thirdly, the dose response curve plateaus at a single dose of 1mg/kg, and if a drug is dosed once a half-life, it will accumulate to produce a peak equivalent to double the peak of a single dose, and a trough equivalent to the peak of a single dose. The skilled person would have expected from DE001 that the maximum therapeutic effect would be obtained even with 0.5mg/kg given every two weeks (once a half-life), so even the lowest dose in the DE003 study would produce the maximum response. DE003 would add little to this expectation, but it certainly would not detract from it.

(iii) Subcutaneous study (DE004)

249. Kempeni 1999 reports that the safety and efficacy of weekly subcutaneous administration of 0.5 mg/kg D2E7 was evaluated in 24 patients with active RA in a placebo controlled trial. It refers to Schattenkirchner 1998 which describes further the DE004 trial. This was a double blind study in which patients received 0.5 mg/kg weekly doses of D2E7. The dose was increased to 1.0 mg/kg weekly for non-responders or those losing their responder status (responder status being a drop in DAS of ≥ 1.2, as reported in Schattenkirchner 1998).

250. Kempeni 1999 was enthusiastic about the results of the DE004 trial. It said:

> "Based on preliminary data, plasma concentrations of D2E7 after multiple subcutaneous doses were comparable to those

> achieved ·with intravenous administration. Up to 78% of patients achieved a DAS/ACR 20 response after three months of treatment with subcutaneous D2E7. With the exception of mild and transient injection site reactions, adverse events occurred with the same frequency and distribution in the D2E7 and placebo groups. The investigators concluded that D2E7 given subcutaneously was safe and as effective as when administered intravenously demonstrating that subcutaneous self adminis- tration is a promising approach for D2E7 delivery."

This is an accurate summary of Schattenkirchner 1998 and reflects the conclusions of the authors of that abstract.

251. AbbVie criticises the DE004 study and suggests that the skilled person would put little weight upon it. In particular, it alleges that since there is only one drug regimen, no conclusions can be drawn about the relative merits of different doses. I agree, but that is not the point of the study, which is to compare s.c. and i.v. regimens.

252. In addition, AbbVie point out that DE004 is based only on 'preliminary' data. Further, it is unclear what the comparator is, since there is no other study in which D2E7 is given weekly i.v. at 0.5 mg/kg (or 1.0 mg/kg for those up-dosed). Finally, all it says is that the plasma concentrations are 'comparable'.

253. I have had regard to all of these points, but I do not agree that DE004 provides too thin a basis for considering that s.c. and i.v. treatment can be considered as comparably effective. Of course, the skilled person would not consider that this had definitely been established, but would have been encouraged by the results, and would consider that there was a good prospect that this would prove to be the case. There was no reason to distrust or reject the conclusions of the investigators that "D2E7 given subcutaneously was safe and as effective as when administered intravenously demonstrating that subcutaneous self-administration is a promising approach for D2E7 delivery."

(iv) The methotrexate study (DE010)

254. A further study is described in which patients who are already taking stable doses of methotrexate are given a single 1 mg/kg dose of D2E7. No abstract is referenced which describes this study further. Kempeni 1999 states that:

> "D2E7 (1mg/kg as a single subcutaneous or intravenous injection) was evaluated in a randomized, double blind, placebo controlled trial in patients whose stable dose of methotrexate was insufficient to control symptoms. An ACR20 response was seen in 67% and 72% of patients receiving D2E7 by subcutaneous and intravenous injection, respectively. The safety profile of D2E7 administration was comparable to that of placebo. Collectively, these early data suggest that the fully human anti TNFα mAb D2E7 is safe and effective as

> monotherapy or in combination with methotrexate when administered by single and multiple intravenous and subcutaneous injections."

255. AbbVie criticises the DE010 study on the basis that no steps would be taken based on this very brief and unsupported account. I disagree. The skilled person would take from the description of the study exactly what Kempeni 1999 suggests; that D2E7 is safe and effective as monotherapy or in combination with methotrexate when administered by single and multiple intravenous and subcutaneous injections. Of course, this would not be conclusive, but would create a good expectation that it was correct.

256. The skilled person would not have been surprised to see that D2E7 had been tested in combination with methotrexate. Infliximab had already been licensed in combination with methotrexate. Prof Johnston's evidence, at [8.11] of his first report, was that in practice, particularly in severe disease, patients may already be receiving one drug but it may not be relieving symptoms fully. Provided that the two drugs do not interact with one another, the combination is unlikely to affect the pharmacokinetics of either molecule. I accept this evidence. Kempeni reports no interaction between methotrexate and D2E7, nor does it report any additional adverse effects from co-administration with methotrexate. *Conclusion of Kempeni 1999*

257. Kempeni 1999 concludes as follows:

> "Collectively, these early data suggest that the fully human anti-TNFAE mAb D2E7 is safe and effective as monotherapy or in combination with methotrexate when administered by single and multiple intravenous and subcutaneous injections. Additional studies are underway to further define optimal use of this novel treatment."

258. In my view, the skilled person would consider that this was a fair summary of the data reported in Kempeni 1999. Whilst, as the author indicates, these are early data, they certainly provide considerable cause for optimism.

Lack of inventive step – legal principles

259. The legal principles of relevance to the present case are well settled, and only require a brief summary:

i) Obviousness must be considered on the facts of each case and the Court must consider the weight to be attached to particular facts in the light of all the relevant circumstances. These include the motive to find a solution to the problem that the patent addresses, the number and extent of possible avenues of research and the effort involved in pursuing them; *Generics (UK) Ltd v H Lundbeck AS* [2007] RPC 32 per Kitchin J, approved by the House of Lords in *Conor Medsystems Inc v. Angiotech Pharmaceuticals Inc* [2008] UKHL 49, [2008] 4 All ER 621, [2008] RPC 28 at [42].

ii) If a particular step is obvious in the light of the prior art, it is not rendered any less obvious merely because there are a number, and perhaps a large number,

of other obvious routes as well; *Brugger v Medicaid (No.2)* [1996] RPC 635 at 661.

iii) If the patentee chooses to advance broad claims, the inventive concept will be broadened in an equivalent way. The question to be answered is whether anything falling within the scope of the claims is obvious; *Brugger* (supra) at 656-657.

iv) Where it is alleged that a step is obvious to try, the question is whether the skilled person would do so with a fair expectation of success; how much expectation depends on the particular facts of the case. Including something in a research project is not enough to establish lack of inventive step; *Conor v Angiotech* at [42]; *Medimmune v Novartis* [2012] EWCA Civ 1234 at [90] - [91]; *Teva UK Ltd v LEO Pharma AS* [2015] EWCA Civ 779 at [32].

The Claimants' case of obviousness in the light of Kempeni 1999

The skilled rheumatologist

260. The obvious route to pursue dosage regimens for D2E7 in the light of Kempeni 1999 was explained by Prof Edwards in his first report, as follows:

261. First, the rheumatologist would have much preferred subcutaneous administration, which Kempeni had shown to be safe and efficacious and which is more convenient than i.v. administration.

262. Secondly, in terms of the dosing interval, Kempeni 1999 reports that the half-life of D2E7 is 11.6-13.7 days; the therapeutic response peaks at 1-2 weeks; symptoms return sufficiently to warrant re-dosing after 2.5 weeks; and a two week interval produced "good" responses.

263. It was therefore clear from Kempeni 1999 that a one or two week dosing interval would be efficacious (dosing at irregular intervals, such as every 12 days, would be highly undesirable as it is more difficult for patients to remember when to take their medication and this might affect compliance). A two week interval would be an obvious time interval to use and a likely obvious first choice for a number of practical reasons:

i) The rheumatologist would prefer infrequent dosing as patients inherently dislike injections.

ii) Fewer syringes would have to be filled, packaged, delivered and administered. Less frequent dosing would create practical advantages in this respect.

iii) Experience with etanercept had shown the potential for injection site reactions, which cause red areas to appear on the patient which can be painful and can take many days to disappear.

iv) A longer dosing interval would represent a practical improvement over etanercept (which was then dosed twice a week).

264. Thirdly, in selecting the dose, the rheumatologist would have wanted to administer the minimum amount of drug capable of producing the maximum therapeutic effect – to ensure patients received a sufficient amount of drug, but to avoid wasting expensive drug and exposing patients to high doses of a drug with unknown long-term side effects. These are matters on which the rheumatologist may have consulted with a clinical pharmacologist.

265. Fourthly, the rheumatologist would note that the dose response curve plateaus at a single 1 mg/kg dose. When designing a treatment regimen using multiple doses, less than 1 mg/kg could be administered to achieve the same therapeutic effect owing to the accumulation of drug (which occurs when patients are given a further dose before the previous one has entirely left their system). In 2001, and still now, it was generally understood that with repeated dosing once a half-life, this accumulation will mean that each dose is effectively equivalent to double a single dose (i.e. 0.5 mg/kg every half-life would accumulate to be equivalent to a single dose of 1mg/kg). As DE003 tested doses of 0.5mg/kg and 1mg/kg in a two week dosing regimen (in the first part of the extension study), those doses (particularly 0.5mg/kg) would have been of the most interest.

266. Fifthly, the rheumatologist's preference would have been to administer D2E7 in fixed doses (a fixed mg amount), rather than variable (mg/kg) dosing, because it is much easier and cheaper to prepare and distribute fixed s.c. doses, rather than preparing syringes with variable doses on a patient-by-patient basis. Individually tailored dosing is more prevalent in early drug development when solutions are made up on site and administered i.v., or if there are toxicity concerns which require the administration of only the exact amount of drug required. As D2E7 has a wide therapeutic window, a fixed dose could be used (as was the case with etanercept).

267. Sixthly, to convert a variable dose into a fixed dose, the skilled team would have taken into account the average weight of an RA patient, which is typically (depending on the patient population) taken as between 70 and 75kg, between which 72kg is a reasonable approximation. They would have then multiplied up the amount of drug needed and picked a sensible round number based upon that calculation. With doses of 0.5mg/kg and 1mg/kg and an average patient weight of 72kg, multiplying by 0.5 and 1 would give 36mg and 72mg. Taking a pragmatic approach, the skilled team would reasonably have rounded these up to 40mg and 80mg.

268. Seventhly, based on the study reported in Kempeni 1999, the rheumatologist would have considered that D2E7 would be effective when given in combination with MTX.

269. Based on this reasoning, Prof Edwards concluded that:

> "Based on Kempeni 1999, the skilled team would have been interested in D2E7 being taken forward as a subcutaneous treatment. Based on my reasoning above, I believe 40mg given every two weeks would have been an obvious dose to choose. The Rheumatologist would also have been keen to see D2E7 with MTX. The skilled team would have had a very high expectation that this regimen, being a variation on the regimen

> already reported as effective by Kempeni, would be efficacious in the treatment of RA. The skilled team may have also been interested in a two week dosing interval with a dose of 80mg and a lower dose, perhaps 20mg, to confirm 40mg is at or near the point of plateau of the dose response curve."

The skilled pharmacologist

270. Prof Johnston reached the same conclusion as to dosing regimens in the light of Kempeni 1999, from the perspective of the pharmacologist. A summary of his reasoning is as follows:

271. From the perspective of the pharmacologist, the following is key information in Kempeni 1999: the single dose response curve reaches a plateau at 1 mg/kg; doses up to 10 times the plateau (10mg/kg) can be administered safely; the half-life of D2E7 is around 12.7 days; the maximum effect is seen 1-2 weeks after initial administration; treatment every two weeks across a number of doses appeared to be sufficient for patients to obtain a "good" response, and symptom flare-up typically occurred after around two and a half weeks; subcutaneous and intravenous administration appear to have similar efficacy and safety profiles; and the combination with methotrexate appears to be safe.

272. From this information Prof Johnston believes the skilled team would consider that Kempeni 1999 shows that D2E7, when administered in an appropriate dosing regimen, would have good prospects of successfully treating RA. In his opinion, the skilled team would be most interested in dosing regimens that had the following properties:

273. First, subcutaneous administration**.** The skilled team would be well aware that subcutaneous dosing is more convenient for the patient and less costly to administer than intravenous dosing, particularly where long term use is anticipated, as in RA. Further, the "phase 1" data showed it to be safe and comparable to intravenous administration.

274. Secondly, infrequent dosing**.** The skilled team would be conscious that infrequent dosing is likely to be preferable given that D2E7 has to be administered with a needle. Kempeni 1999 would suggest to the skilled team that either weekly dosing or dosing every other week is suitable to obtain a "good" response. These intervals are convenient and easy for a patient to remember. Dosing every other week would be considered preferable as it involves fewer injections. The half-life, as explained above, also supports a two week dosing interval.

275. Thirdly, dose size. The DE001 study in Kempeni 1999 found a single dose of 1mg/kg to be at the plateau of the dose response curve. To achieve a steady state accumulation after 5 half-lives in a multiple dose regimen that is equivalent to a 1mg/kg single dose, one would require 0.5mg/kg per half-life (approximately every two weeks). For a dosing interval of one week, a lower dose would be required.

276. Fourthly, fixed dose. In Prof Johnston's opinion, fixed doses of drugs are more convenient than variable doses. Converting 0.5mg/kg to a fixed dose (assuming an average patient weight of around 72kg) would give a dose of 0.5 x 72 = 36mg. In practice, Prof Johnston would expect this to be rounded up to 40mg.

277. Prof Johnston therefore considers that this would lead the pharmacologist to consider that 40mg every two weeks was an appropriate dosing regimen to take forward, with a good prospect that it would be safe and efficacious.

Absence of collusion

278. Whilst the reasoning of Profs Edwards and Johnston appears similar, their first reports were prepared independently of each other. Each expert was asked to advise on appropriate dosing regimens in the light of the prior art. They were only shown each other's reports after they had formed their views. AbbVie submits that this was a flawed approach, in that the pharmacologist would first need to be given the clinical target for the dosing regimen by the rheumatologist. I do not accept this submission. In my judgment, it is important that two experts came to the same view based on the prior art independently of each other. This lends force to their conclusions that this was an obvious dosing regimen.

279. Prof Edwards knew the approved dosing regimen for Humira, and I am conscious of the need to guard against hindsight. However, having heard his evidence, I am satisfied that he was able to exclude such knowledge from his mind and approach the prior art objectively, from the perspective of the ordinary rheumatologist skilled in the art. I also regard it as significant that Prof Johnston had no idea of the dosing regimen for Humira, and did not ask Prof Edwards about it. Indeed, he arrived at the 40 mg sc eow dosage regime from a consideration of Kempeni 1999, without any idea that D2E7 was Humira. So he had no clue as to any target to aim at. Furthermore, he did not regard the task as a difficult one, but considered that the conclusion came out of the data very simply. This, in my view, is powerful corroborative evidence of obviousness in the light of Kempeni 1999.

AbbVie's answer to obviousness in the light of Kempeni 1999

The "ten day point"

280. This became a major issue in the case, as a result of certain answers given in cross-examination by Prof Edwards. In the context of the statement in Kempeni 1999 that "the therapeutic effects… reached the maximum effect after 1-2 weeks, with a dose response reaching a plateau at 1mg/kg" he was asked the following; 2/213/21 – 214/8:

> "Q. You certainly cannot draw the conclusion, can you, professor, from this data that 14 days the concentration of drug following a 1 mg dose is sufficient to maintain beyond the plateau of the concentration response curve?
>
> A. I do not think you can be absolutely sure of that on the basis of assuming the simplest default model that would explain the data, and we are told about one to two weeks, so maybe ten days, so I would

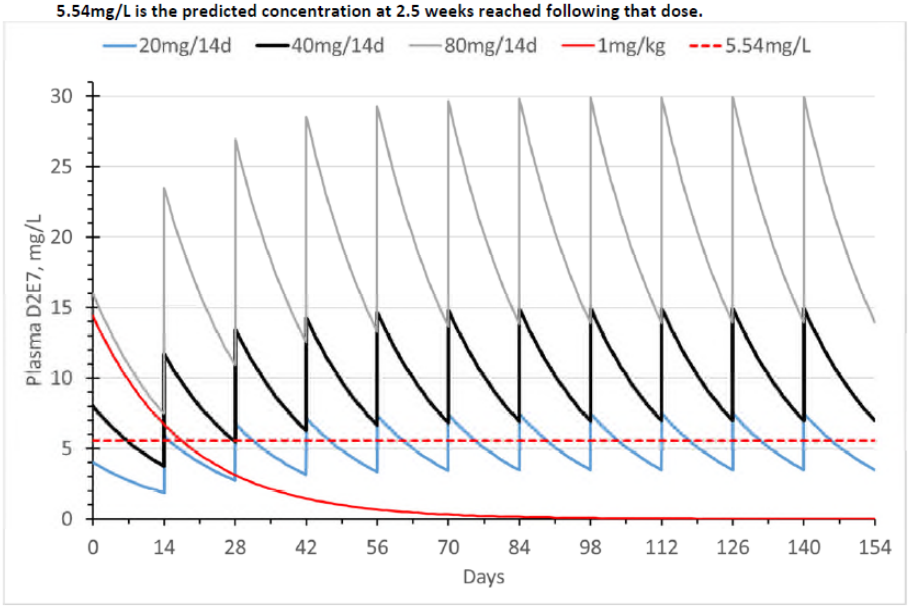
work on the model that these responses told us something about the efficacy of the level of drug that was still around at about ten days, which is a little bit less than a half-life."

281. So, when asked about the length of time that the drug concentration would be likely to remain in the blood to achieve the required dose response, Prof Edwards estimated 10 days.

282. The reason why this matters is as follows: Prof Johnston arrived at a dosage regimen of 40mg sc eow from the information in Kempeni 1999, by a simple process of reasoning, which I have summarised above. He then illustrated his analysis by way of a graphical model using, amongst other things, the 2.5 week interval from DE003. He explained that this was just an alternative way of presenting his analysis. AbbVie submits that if one applies the 10 day interval, instead of the 2.5 week interval, to Prof Johnston's model, the troughs drop below the required level, indicating that 40mg sc eow will not work. This, says AbbVie, is fatal to the Claimants' case. AbbVie's submissions are as follows:

i) Prof Johnston first plotted the expected plasma concentration/time curve for a single 1 mg/kg dose (chosen because such a dose is on the plateau in DE001). This is the red curve in his Fig. 2, shown below:

Figure 2 **Predicted plasma D2E7 concentrations over 154 days in a 72kg patient following 20, 40 and 80mg iv doses given every 14 days. For reference the concentration after a 1mg/kg single dose is shown, and the dotted line at 5.54mg/L is the predicted concentration at 2.5 weeks reached following that dose.**



ii) He then worked on the assumption that the concentration following a 1 mg/kg single dose remains above the concentration needed to produce the desired therapeutic effect for 2.5 weeks (on the basis of the DE003 study).

iii) He could therefore read off the concentration which he considered corresponds to the minimum level required to maintain the desired therapeutic effect, being the concentration 2.5 weeks after a single 1 mg/kg dose, which is 5.54 mg/l.

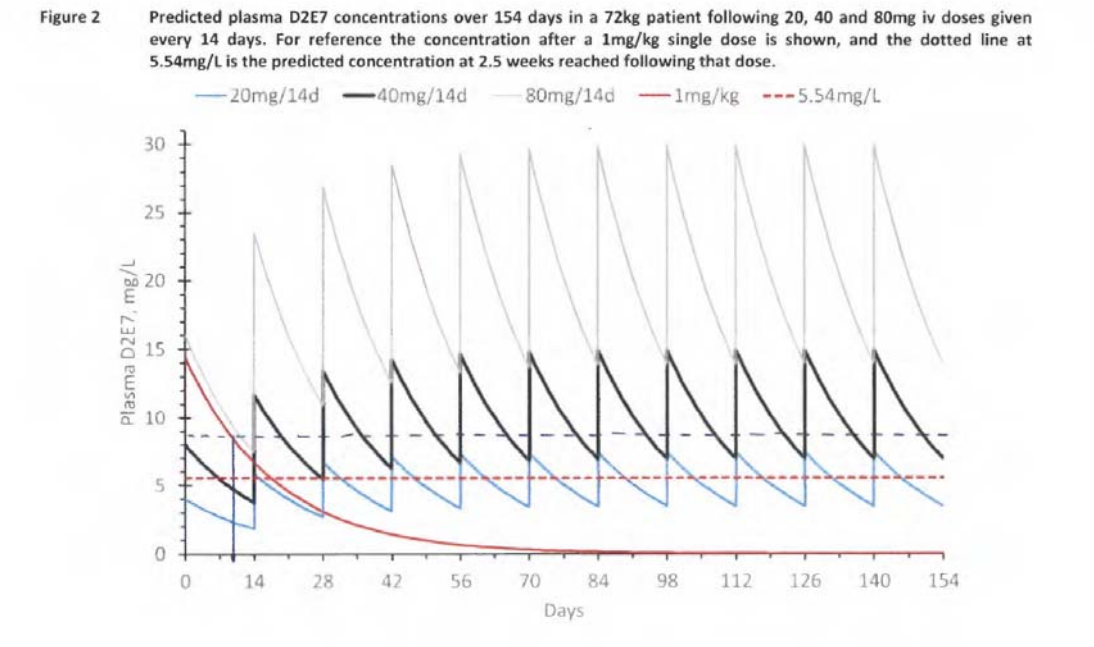
This is indicated by the horizontal dashed red line on Fig. 2. As he explained, one would want the concentration to remain above the minimum to allow for patient variability.

iv) Prof Johnston was then able to plot out the expected plasma concentrations for 20, 40 and 80 mg eow to see whether they maintain the concentrations at or above what he said was the required level, which can also be seen in Fig. 2 above.

v) In his first report at [8.21], Prof. Johnston expressed the view that based on this modelling Fig. 2 illustrates that the 40 and 80 mg eow regimens would work, whereas the 20 mg eow regimen would be expected to fail since the troughs drop below the required concentration at steady state.

vi) However, Prof Edwards' evidence leads to the conclusion that 40 mg eow would also be expected to fail. Prof Edwards' evidence was that the concentration produced by a single 1 mg/kg dose after 10 days was at the plateau of the concentration response curve. The aim is to keep the trough concentration above that required to be on the plateau. So, to identify the trough concentration needed (even for an average patient) one needs to use the concentration 10 days after a single 1 mg/kg dose, not the concentration 2.5 weeks after such a dose.

vii) If that is done, one arrives at an altered version of Prof Johnston's Fig. 2 [X/6] which is reproduced below, the black dotted line having been inserted by Mr Tappin. The troughs at 40 mg after 14 days drop below this line:



viii) AbbVie then relies on the cross-examination of Prof Johnston at 3/403/21 – 404/16. When shown the diagram at X/6, Prof Johnston accepted that if the pharmacologist was told by the rheumatologist that the concentration at about

day 10 was "the key one", instead of that at 2.5 weeks, the pharmacologist who drew the X/6 diagram would conclude that the 40 mg every other week dose was too low, because the troughs go below that concentration. It would not achieve the therapeutic aim at that concentration, if the line was drawn as shown in X/6.

ix) AbbVie's conclusion was that the pharmacologist would predict that a 40 mg eow dosing regimen would achieve the necessary plasma concentrations for only the first 10 days of each 14 days of the regimen, and would fall too low for the last 4. 40 mg eow is therefore expected to be too little (and/or the interval too long).

283. This is an attractive submission, which was developed with great skill by Mr Tappin. However, in the end, I do not accept it, for the following, cumulative, reasons:

The way in which the 10 day point emerged in evidence.

284. Mr Waugh submits that AbbVie had the evidence in chief from the Claimants' experts setting out the assumptions on which Prof Johnston's graph was prepared for weeks before the trial as it was served on 8 November 2016. He points out that nothing was said by either of AbbVie's experts in reply to suggest that Prof Johnston's graph was wrong, on the basis now advanced by X/6. Insofar as this is intended to suggest that Mr Tappin was not entitled to take the 10 day point, I reject this submission. The 10 day figure was volunteered by Prof Edwards during his cross-examination. Further, Prof Boddy did respond to Prof Johnston's graph, at [31] of his second report. He suggested that the skilled pharmacologist would not have considered Prof Johnston's calculations to be at all meaningful, for the following (amongst other) reasons:

> "Prof Johnston sets out his calculations in Exhibit ACJ-3. The skilled pharmacologist would not have considered these calculations to be at all meaningful because they are based on assumptions as to the pharmacokinetics and pharmacodynamics of D2E7 that are not supported by the Cited Art (or for that matter the Additional Art). In particular:
>
> …..
>
> 31.3 Prof Johnston assumes that an appropriate target trough concentration is the concentration that would be produced by a single 1 mg/kg dose after 2.5 weeks. The purported basis for this assumption (see paragraph 7 of ACJ-3) is that *"the ascending dose study indicated that on average symptoms returned after 2.5 weeks"*. However, as I have explained in paragraph 25 above, the 2.5 week average dosing interval in that study related to the entire patient population, the majority of whom had received doses (potentially multiple doses) of greater than 1 mg/kg (up to 10 times greater). As I explained in paragraph 21 above, there is no basis in the Cited Art (or Additional Art) for the skilled pharmacologist to assume that a

> single dose of 1 mg/kg would maintain the plateau level of response over a 14 day dosing interval."

285. So, Prof Boddy did criticise Prof Johnston's reliance on the 2.5 week average figure, and the assumption that a single dose of 1 mg/kg would maintain the plateau level of response over a 14 day period. However, it is important to appreciate the context in which he made these observations. Prof Boddy was saying that there was insufficient information in the prior art, including in DE003, to perform the calculations illustrated by Prof Johnston's graph (a contention which he elaborated at [21] and [25] of his evidence). Therefore, his point was not that an alternative graph, such as that shown in X/6, was appropriate, but rather that the whole exercise was unreliable. AbbVie's case has now shifted, and it positively relies on X/6, which was not supported by its expert evidence. To that extent, Mr Waugh's point is well founded.

Consistency with AbbVie's case

286. The way in which this evidence was presented by AbbVie has a further consequence. I am not satisfied that the graph at X/6 is consistent with AbbVie's case. I have referred to the cross-examination of Prof Johnston concerning X/6 (at the time X/5). The question that Prof Johnston was asked was as follows:

> "Professor, what I have here is I have taken your figure 2 and put another line on it, as you will see. If the pharmacologist was told by the rheumatologist that the concentration at about day 10 was the key one, instead of that at two and a half weeks then obviously you would end up drawing a line on our model for C min, as shown in this diagram, X5, that I have just handed up. If that were the right conclusion, then the pharmacologist would have to say that the 40 mg every other week dose was too low."

287. The hypothesis was that the pharmacologist would be told by the rheumatologist that the concentration at about 10 days was "the key one". On this hypothesis, Prof Pope should have told this to Prof Boddy. But there is no suggestion whatsoever in any of the evidence that she did so. Nor was it advanced by Prof Boddy.

Reliability of the 10 day estimate

288. The Claimants further submit that because the graph at X/6 and the placing of the black dotted line were generated for the first time in cross-examination, the 10 day response by Prof Edwards was given "on the hoof" and was not a considered response which could be relied on as an accurate assessment. They rely on the observation of Birss J said in *Actavis v Lilly* [2016] EWHC 1955 (Pat) at [304]:

> "I will also add this. One of the vices of raising a point like this in cross-examination when it is not foreshadowed in the expert evidence is that it can become a test of how quickly people can think. That is not helpful."

289. I have noted that, on occasion, Prof Edwards was anxious to agree with the cross-examiner, in circumstances where, if he had had more time to reflect, he might have given a somewhat different answer. 10 days was not a figure that initially was suggested to him. However, at 2/218/5-13 he said:

> "My best guess would be somewhere between 1 and 2, so that is 10-11 days. We might say that may be a little bit shy of a half-life, but I actually think that if they say that these responses have peaked at 1-2, from my experience of this situation I would have expected most patients really to be maintaining that at two weeks, but that is arbitrary. I am working on the assumption that this is somewhere around 10-12 days, on the basis of being one to two weeks. So, it is the least biased interpretation, if you like, from what we have."

290. This evidence, although not entirely clear, suggests that Prof Edwards considered that most patients would maintain the dosage response at 14 days, but, as a very fair witness, was prepared to assume 10 - 12 days. It does not suggest that it is a hard and fast value upon which reliance can be placed.

Confusion between the parameters of "dose" "response" "concentration" and "therapeutic effect" and how they change over time

291. The Claimants allege that the graph at X/6 confuses concentration v time with dose v response and therapeutic effect v time. They emphasise that Prof Johnston's graph shows the expected plasma concentration of D2E7 over time, and nothing more. The 1 mg/kg single dose shows a simple decaying line. The 20, 40 and 80 mg repeat dose regimens show "saw-tooth" profiles with "peaks" and "troughs" – but care is needed to distinguish these "peaks" of concentration from the "peak" in therapeutic effect. It is necessary initially to set out where data are present and absent in the evidence:

i) There are data for dose v response, as reported in Kempeni 1999 in relation to DE001.

ii) There are no data for concentration v response: Prof Boddy showed stylised curves in his first report at figure 19. But, for D2E7, there are no data in the case which is, or has been, fitted to a concentration-response curve.

iii) There are some data for therapeutic effect v time: Kempeni 1999 (DE001) refers to a "maximum effect after 1-2 weeks" and van de Putte says the therapeutic effect "peaked at week 1-2". However, there is no graph, or other depiction of how therapeutic effect changes over time.

iv) The time of the peak therapeutic effect is not the time at which flare happens. The evidence was that therapeutic effect does not fall off a cliff and that the responses were maintained beyond the peak. This is supported by Prof Boddy's evidence at [31.4]. When suggesting that Prof Johnston's graph was not meaningful, he made clear that there would be a lag time between concentrations falling below the effective level and the loss of clinical

response. Therefore, X/6 does not indicate when clinical response would be lost. Prof Boddy said:

> "Prof Johnston assumes that response status is lost immediately after the plasma concentration drops below an effective level. The skilled pharmacologist would not assume that to be the case. There is no information available about the relationship between declining plasma concentration and loss of response. Among a number of potential scenarios, the skilled pharmacologist would consider that there would be some lag-time between concentrations falling below the effective level and the loss of clinical response."

292. Mr Waugh submits that confusion arose during the cross-examination of Prof Edwards due to the muddling of the parameters of 'dose', 'response', 'concentration' and 'therapeutic effect', and how they all relate to each other and change over time. He gave a number of examples of this. First, Prof Edwards' answer "maybe 10 days" arose from a discussion about peak therapeutic effect, not concentration. When asked where the peak would be for lower doses, his view was that the therapeutic effect would peak at the same time for all doses; 2/212-214. However, at 2/226/25 it was put to Prof Edwards that the 10 day estimate "would lead you to say that at about ten days the concentration yielded by 1 mg/kg single dose is at the plateau of the concentration response curve." It is said that there are significant problems with this question:

293. First, the question disregards that Prof Edwards gave the "ten day" answer in relation to peak therapeutic effect, not concentration. There is no "concentration response" curve arising from any of the data. Secondly, a 10-day figure cannot be put on a concentration response curve (or on a dose response curve) – neither curve has any time axis/time element. Thirdly, Prof Edwards replied: "It is a dose which would correspond to a point on the plateau." This appears to be a reference to the 1 mg/kg dose in the question, and the dose response curve arising from DE001, and not to X/6.

294. A further example of confusion is said to have arisen at 3/257-258. It was put to Prof Edwards that: "Your position was that on the basis of the DE001 study that we were looking at in van de Putte and Kempeni 1999, the concentration at the plateau response curve is that produced by a single 1 mg/kg dose after ten days". The Claimants point out that there is no such thing as a "plateau response curve" and no such curve had been mentioned in the case. The question may have been intending to refer to a "dose response curve", but neither concentration nor time can be put onto such a curve. Prof Edwards replied that he did not use those terms, and repeated his original point that "it is the minimum effective dose" which must be a reference to the "1 mg/kg dose" in the question.

295. I consider that there is force in the Claimants' points, particularly because the 10 day point had not appeared in any of the written evidence. It seems to me that a graph prepared for one purpose was being used to illustrate a quite different point, and this led to confusion between concentration, time, response curves and therapeutic effect.

Did Prof Edwards accept that 14 day administration of 40 mg sc was inappropriate?

296. This, in my judgment, is a crucial question. If, in the light of the 10 day point, Prof Edwards had accepted that the dosage regimen that he considered obvious would be too low, then this would have clearly made the point that AbbVie now seeks to rely on. In fact, that proposition was never put to him. Furthermore, subsequent to the cross-examination concerning X/6, he maintained his position that 14 days remained the reasonable period of administration; for example, at 3/272 – 275 and 3/315. Prof Edwards, throughout his evidence, made clear that 0.5 mg/kg every 14 days, or 40 mg sc eow would have been the obvious dosage regimen to pursue, and that he would have included doses of 20mg and 80 mg sc eow as comparators. I should add that Prof Johnston also maintained his position as to this dosage regimen, in spite of the 10 day point, and it was not put to him that this was unsustainable.

297. In the light of the way in which this evidence emerged, uncertainty about the reliability of the 10 day figure, and confusion in the questioning, in my view it would have been essential for AbbVie to draw the threads together and establish how it impacted on the key question in the case. It did not do this.

A lion in the path

298. No-one has suggested that, in reality, 40 mg sc eow is too low a dose or is in any other way an inappropriate dosing regimen for adalimumab. On the contrary, the Summary of Product Characteristics for Humira specifies or includes this very dosage regimen for a number of conditions, including RA. Therefore, if the skilled person had prepared the graph as shown in X/6, and had considered that 14 days was an inappropriate period for a 0.5 mg/kg dose, he would have been badly mistaken. It would therefore have constituted a "lion in the path" which would have deterred him from pursuing that dosage regimen.

299. Mr Waugh has reminded me, in the context of other arguments advanced by AbbVie, of the observations of Jacob LJ on lions in the path, or paper tigers, in *Pozzoli SPA v BDMO SA and others* [2007] EWC Civ 588; [2007] FSR 37:

> "27 Patentability is justified because the prior idea which was thought not to work must, as a piece of prior art, be taken as it would be understood by the person skilled in the art. He will read it with the prejudice of such a person. So that which forms part of the state of the art really consists of two things in combination, the idea and the prejudice that it would not work or be impractical. A patentee who contributes something new by showing that, contrary to the mistaken prejudice, the idea will work or is practical has shown something new. He has shown that an apparent "lion in the path" is merely a paper tiger. Then his contribution is novel and non-obvious and he deserves his patent.
>
> 28 Where, however, the patentee merely patents an old idea thought not to work or to be practical and does not explain how or why, contrary to the prejudice, that it does work or is practical, things are

> different. Then his patent contributes nothing to human knowledge. The lion remains at least apparent (it may even be real) and the patent cannot be justified."

300. The evidence in relation to X/6 does not establish that it represents a technical prejudice in the art. Nor does it establish that any of the patents concerning this dosage regimen overcame any such prejudice. Therefore, it does not refute the propositions sought to be established by the declarations in the present case.

Anti-drug antibodies (ADAs)

301. AbbVie relies on the fact that the effect of ADAs can include a reduction in efficacy over repeated administrations, meaning that the clinical response to the first dose may not be replicated in later doses, and the half-life may also decrease. As far as fully human antibodies are concerned, AbbVie claims that it was a hope, rather than an expectation that they would reduce the risk of ADAs. Prof Pope said, at [3.48] of her first report, that:

> "It was known at the Priority Date that humanisation of a non-human antibody would not fully eliminate the risk of an immune response, and it would have been anticipated that even completely human biologics could be immunogenic. By way of example, it was widely known that recombinant human insulin (i.e. insulin made from a human gene expressed in cells grown in a laboratory) could induce ADAs. Therefore, a Skilled Clinician reading about a fully human antibody at the Priority Date would have been concerned about the possibility of an ADA response and would have had that in mind when considering a dosing regimen for such an antibody."

302. I do not accept this evidence. Prof Johnston was clear that whilst antibodies were something to watch out for, and might require subsequent modification of the dosage regimen if they presented a problem, there was no reason to alter the dosage regimen in anticipation of such a problem. Prof Boddy agreed that Prof Johnston's approach was sensible and pragmatic and that there was no a priori reason to take steps to compensate for an immunogenic response.

303. This is particularly the case with D2E7, which was a fully human antibody, and, as emphasised in Kempeni 1999, was thought likely to reduce ADA concerns. This was not certain, as it was known that the humanisation of a non-human antibody would not fully eliminate the risk of an immunogenic response. However, there was a fair expectation that this would be the case, and this was a positive advantage of D2E7. Furthermore, there was no evidence of any ADA reactions from the trials reported in Kempeni 1999.

The Additional Prior Art

304. Prof Pope suggested that, in the light of the Additional Prior Art, the skilled person would consider that the most promising avenues were either intravenous

administration every other week at high doses (3-5 mg/kg or higher), or subcutaneous administration once weekly starting with a lowest dose of 1 mg/kg.

305. In its closing, AbbVie decided to focus on only four of the additional abstracts: (i) den Broeder (389) relating to DE003; (ii) Rau (907) relating to DE010; (iii) van de Putte (1218) relating to a further trial known as DE007, described in Kempeni 2000; and (iv) Weisman relating to a further study known as DE005. I shall now consider all of these abstracts, save for van de Putte (1218), which I deal with in the context of Kempeni 2000.

den Broeder (389) – DE003

306. This is an abstract reporting on about one third of the patients in the DE003 study. This was a subset of patients at the Nijmegen centre of Dr van de Putte. AbbVie contends that the abstract is relevant for its observation that "[a]fter a dose escalating phase eventually all patients were treated with 3.0, 5.0 or 10.0 mg/kg iv". The study involved the randomisation of patients into each group, so there would be expected to be about 8 in each arm, and 8 patients in the 0.5 mg/kg arm. AbbVie submits that, given that the skilled reader would have known from Kempeni 1999 that in DE003, D2E7 was administered to patients bi-weekly until they obtained a 'good' response, but were up-dosed if they failed to respond well, it is clear that all the patients on 0.5 mg/kg and 1 mg/kg eow failed to respond well. Prof Pope's view was that this was significant and indicated that 0.5 mg/kg eow was too low a dose.

307. I do not agree that any such conclusion would have been drawn by the skilled person from den Broeder. This was an open (un-blinded) study and Prof Edwards explained, and I accept, that it was inappropriate to draw any conclusion about dose response from it. He stated at 3/262/10-18:

> "… that there will be a motivation for the patients to put down a score on their global health which we have reason to believe will mean that they have a slightly higher dose because they are not necessarily feeling absolutely as well as they might want to. So when you have an option of moving up and not moving down in this sort of study, I personally would not take any notice at all of how many people moved up or what was going on because we are in a situation where there is room for systematic bias and systematic bias always creeps into this sort of study."

308. Furthermore, Dr Kempeni had access to all of the data available, including den Broeder, when he reported on the D2E7 trials in Kempeni 1999. Den Broeder represents a small subset of the data available to Dr Kempeni, and he did not draw the conclusion from it that is advanced by Prof Pope. As the rheumatologist with oversight of all the available data and overall responsibility for the trials, had this conclusion been justified, I consider that Dr Kempeni would have been obliged to draw attention to it.

Rau (907) – DE010

309. Rau (907) expands on the data obtained in the placebo controlled part of the DE010 study referred to in Kempeni 1999. AbbVie contends that it highlights differences in efficacy results between the two arms, i.v. and s.c. Kempeni 1999 had reported only on the ACR20 response rates for the two arms; namely 67% and 72% for s.c. and i.v. respectively. Rau (907) additionally reports on the DAS response rates – 72% for i.v. against 44% for s.c. (with a placebo response of 28%). Prof Pope considered that these results with the i.v. administration were "demonstrably better than the subcutaneous results after a single dose".

310. I do not accept that the skilled person would consider that i.v. administration, rather than subcutaneous administration, was to be preferred in the light of Rau (907). Prof Edwards explained that it would be very surprising for subcutaneous treatment to be less effective than i.v. treatment, and that he considered the ACR20 response rates to be a preferable measure to the DAS response rates. I accept his evidence. Again, Kempeni 1999 did not suggest that the DE010 trial indicated that i.v. was preferable to s.c. administration – on the contrary, it suggested no material difference.

Weisman (1948) – (DE005)

311. Weisman reports on study DE005, which is not considered in any other document. AbbVie submits that in this study, which involved up-dosing according to clinical response, about half of the patients in 0.25 and 0.5 mg/kg i.v. arms needed to be up-dosed; the results for 3 and 5 mg/kg i.v. eow looked impressively high, with the 5 mg/kg seeming to be even better than the 3 mg/kg group. It argues that this abstract suggests that the lower doses are to be avoided as being inadequate.

312. Prof Edwards was very critical of the Weisman study. He regarded it as a document with an agenda, which was to advocate intravenous usage for D2E7 as it was popular in the United States for financial reasons. Prof Edwards noted the absence of any data about the blinded (as opposed to the unblinded) study in Weisman. Prof Edwards explained that Weisman only reported on an open label study, even though an initial, blinded study was undertaken. This is a notable omission. The bias inherent in open label studies was well known. This explains why Weisman (and den Broeder) did not report on any dose response results in the conclusion, because they would not have been reliable. Prof Boddy accepted that it was basic knowledge that blinding in clinical trials was used to eliminate bias. For these reasons I do not consider that the skilled person would draw the conclusion from Weisman that lower doses are to be avoided, or indeed would draw any reliable conclusion from it.

Prof Pope's proposed dosage regimens

313. Having considered Kempeni 1999, Prof Pope stated at 4.34 of her first report that:

> "In my opinion the obvious regimens for the Skilled Clinician to test in a further clinical trial, in a larger group of patients, would have been intravenous doses of adalimumab in the range of 3-10 mg/kg at a dosing interval of roughly every 2 weeks,

> given that doses in that range appeared from the data available to have the best efficacy without significant adverse effects. The alternative would have been to conduct a dose ranging study for subcutaneous administration of adalimumab, starting with 1 mg/kg adalimumab (as the lowest dose) administered at weekly dosing intervals. These would be the obvious regimens to test whether or not given in combination with MTX."

314. I do not accept this evidence, which, in my view, is based on Prof Pope's preferences, which would not be shared by the skilled person, and appears to reject, rather than follow, the disclosure of Kempeni 1999.

315. Prof Edwards disagreed with Prof Pope's suggestions at [77] – [79] of his second report, and I find that his reasons are compelling. In particular, as to the suggested dosage regimen of 3-10 mg/kg i.v. every two weeks intravenous administration would have been seen as much less attractive than subcutaneous administration, and intravenous administration of adalimumab would have been seen as less attractive than etanercept, which was approved for subcutaneous administration in 2001. The proposed doses appear far too high, when doses of 0.5 and 1 mg/kg would appear to be safe and efficacious. The rheumatologist would avoid administering more drug than necessary, in order to avoid the risk of long-term side effects.

316. As to the suggested dosage regimen of 1mg/kg subcutaneous administration every week, Prof Pope should have considered a fortnightly dosing interval, having proposed such an interval for i.v. use. The skilled person would be encouraged to adopt a fortnightly dosing interval from the disclosure of Kempeni 1999 and consideration of the abstracts. Furthermore, medicines approved for s.c. administration are frequently administered according to a fixed dose and are more cost effective. Prof Pope should have considered the use of a fixed dose in her conclusions rather than only weight based dosing. Finally, Prof Pope should have considered that doses lower than 1 mg/kg (whether fixed or variable) every other week would be obvious to include as part of a further study, in the light of Kempeni 1999 and the abstracts.

Pharmacological issues

317. Prof Boddy's view was that the pharmacologist was not given enough pharmacokinetic or pharmacodynamics information in Kempeni 1999 to assist the rheumatologist in making any reliable predictions as to the plasma concentrations that would result from any particular D2E7 dosing regimen or whether these plasma concentrations would be safe or efficacious. I do not accept that the skilled person would share these reservations, and, for the reasons set out above, I prefer Prof Johnston's view. Furthermore, I have concluded that, on reading Kempeni 1999, the pharmacologist would conclude that D2E7 has simple pharmacokinetics and that it can be treated as a one compartment system.

Other points in relation to Kempeni 1999

318. I have already rejected AbbVie's criticisms of Kempeni 1999, and its submissions that the skilled person would pursue a higher dose, weight based, i.v. or one week only regimen in the light of Kempeni 1999 and the abstracts, including the Additional Prior Art.

Conclusion in the light of Kempeni 1999

319. Having regard to all the circumstances, I consider that based on Kempeni 1999, the skilled team would have taken forward D2E7 as a subcutaneous treatment. 40mg given every two weeks would have been an obvious dose to choose. The combination of D2E7 and MTX was obvious. The skilled person would have had a high expectation that this regimen, being a variation on the regimen already reported as effective by Kempeni 1999, would be efficacious in the treatment of RA. The skilled person would also have been interested in a two weekly dosing interval with a higher dose of 80mg and a lower dose of 20 mg, to confirm that 40 mg was at or near the point of plateau of the dose response curve.

320. On this basis, I conclude that the administration of the Claimants' proposed products in the treatment of RA by a dosage regimen of 40 mg once every two weeks by subcutaneous injection was obvious in the light of Kempeni 1999.

Kempeni 2000

321. Kempeni 2000 reports much of the same content as Kempeni 1999 and provides an update on the development of D2E7. Under the heading "Phase I studies", Kempeni 2000 briefly describes the studies in Kempeni 1999. It records that ACR20 responses were obtained in 56 - 80% of treated patients; and that therapeutic effects were evident in 24 hours to 1 week and reached a maximum effect after 1-2 weeks, with the dose response plateau at 1 mg/kg. Kempeni 2000 then states:

> "Subcutaneously and intravenously administered D2E7 provided similar D2E7 plasma levels and comparable ACR20 response rates. At a dose of 1 mg/kg, subcutaneous and intravenous administrations were safe and efficaceous when given with standard, stable doses of MTX. In the long term open label extensions, a high percentage of patients continued to receive treatment with D2E7 indicating that long term treatment with D2E7 in the dose range from 0.5 to 10 mg/kg was well tolerated."

322. Kempeni 2000 then contains a section headed, "Phase II study", which reports that D2E7 had advanced to Phase II in a double-blind randomised trial of 283 patients, with s.c. dosing. This study moved to fixed dosing. The regimen used was 20, 40 and 80mg, given every week. Kempeni 2000 states that:

> "All three doses of D2E7 were efficacious (49% to 57% of patients received ACR20 responder status compared with 10%

> placebo, p<0.0001) and no dose response relation was apparent at month 3. ”

323. Prof Edwards said in his first report, and I accept, that this shows efficacy for all three doses at a very high level of confidence. Furthermore, the information that "…no dose response relation was apparent at month 3" would have been understood to mean that each fixed dose that had been tested (i.e. 20, 40 or 80mg) was equally efficacious after 3 months of treatment. As there is good reason to use the minimum effective dose, the information that the 20mg dose (weekly, s.c.) appears as efficacious as the higher doses, would have been significant.

324. In addition, the rheumatologist would have found it encouraging to read that patients had been treated for more than 12 months with any adverse events only comparable to those seen with placebo. This indicates that D2E7 had the potential for use as a long-term treatment. It is also reported that D2E7 was moving to phase III trials.

325. The conclusion of Kempeni 2000 was also encouraging:

> “Collectively, these early data suggest that the fully human anti-TNFα antibody D2E7 is safe and effective as monotherapy or in combination with MTX when administered by single and multiple intravenous and subcutaneous injections. Additional studies are underway to further define optimal use of this novel treatment.”

van de Putte (1218) – DE007

326. Van de Putte (1218) reports the 12 month data from the DE007 study (the 3 month ACR20 results of which are summarised in Kempeni 2000). Fixed doses of 20, 40 and 80 mg per week were administered. The results are set out in the table, reproduced below:

% Response or Improvement(3monthss/12 months)

	Placebo	20 mg	40 mg	80 mg
ACR 20	14	49*/46	59*/60	56*/56
ACR 50	3	24*/25	27*/43	19*/31
TJC (median)	8	52*/51	57*/60	53*/60
SJC (median)	15	39*/52	56*/65	54*/59
CRP (median)	1	53*/55	61*/64	64*/60

*p<0.001 when placebo compared to D2E7 (for 3 months)

327. Van de Putte (1218) then states that the three treatment arms are “statistically equally efficacious”. AbbVie contends that this phrase would be understood to mean that they are not statistically different, and further the rheumatologist would understand that the study would not be expected to be powered to detect such differences. My view is that the message is clear – that there were no material differences between the three treatment arms, and statistically they could not be separated. Prof Pope appeared to resist this during her cross-examination at 5/777, on the basis that the phrase

"statistically equally efficacious" is meaningless, but I did not find her evidence helpful on this point.

328. Prof Pope's evidence was that for every clinical outcome measured in the study the 40 mg and 80 mg weekly s.c. doses gave better results than the 20 mg weekly s.c. dose. In particular, after 12 months only 25% of patients on 20 mg achieved ACR50 whereas 43% on 40 mg and 31% on 80 mg did so. Her evidence was that the 20 mg dose had reduced efficacy and would not be pursued.

329. DE007 is, in fact, reported in three abstracts, namely van de Putte (1977), van de Putte (OP-056) and van de Putte (1218), all of which would have been read by the skilled person. These successive abstracts added data as it became available over time. Van de Putte 1977 reported at 3 months of s.c. injections, van de Putte (OP-056) reported at 3 and 6 months and van de Putte (1218) reported the data for 3 and 12 months.

330. The message from each of these abstracts was essentially the same. Van de Putte 1977 reported that "20, 40 and 80mg/week were nearly equally efficacious" after 3 months; van de Putte (OP-056) reported that "20, 40 and 80mg/week were statistically equally efficacious" after 6 months; and van de Putte (1218) reported that "20, 40 and 80 mg/week were statistically equally efficacious" after 12 months. This is the conclusion that the skilled person would take from these abstracts. It is also the conclusion that Dr Kempeni drew in Kempeni 2000 (infra). The attempt by AbbVie to suggest that 20 mg/week would not have been seen as effective is not supported by any of these abstracts.

331. As with Kempeni 1999, Prof Pope suggested that obvious dosage regimens in the light of Kempeni 2000 were either intravenous doses of adalimumab in the range of 3-10 mg/kg at a dosing interval of every 2 weeks, subcutaneous administration of adalimumab, starting with 1 mg/kg adalimumab (as the lowest dose) administered at weekly dosing intervals. Given that Kempeni 2000 reported on further progress for D2E7 from clinical trials in respect of fixed dose, subcutaneous administration, Prof Pope's approach rejects the prior art and substitutes her own views. I do not consider that her opinion would be shared by the person skilled in the art.

The Claimants' case of obviousness in the light of Kempeni 2000

332. The Claimants point out that Kempeni 2000 expressly discloses that fixed doses of 20, 40 and 80mg had been administered weekly by subcutaneous injection and were efficacious with no dose response relationship apparent at month 3. Therefore, the only issue is whether bi-weekly, rather than weekly, dosing was obvious. The answer, according to the Claimants, is plainly in the affirmative.

333. First, there were obvious drivers towards bi-weekly, rather than weekly, dosing and I have accepted Prof Edwards' evidence on this issue. These included a preference for infrequent dosing as patients inherently dislike injections; the fact that fewer syringes would have to be filled, packaged, delivered and administered; the fact that experience with etanercept had shown the potential for injection site reactions; and the fact that a longer dosing interval would represent a practical improvement over

etanercept (which was then dosed twice a week). In considering the dosing interval, the rheumatologist would have noted the information in Kempeni 1999 and repeated in Kempeni 2000. For the reasons which I have discussed above, the rheumatologist would have considered a one or two week dosing interval to be viable as an effective treatment and two weeks would have been preferred.

334. Secondly, the rheumatologist would have considered the 20 mg weekly dose to be of interest as the lowest effective dose in the study. The rheumatologist would also have been interested in a lower dose to ensure that the minimum effective dose had been identified. A lesser amount of drug could be tested either by decreasing the dose amount or increasing the dosing interval.

335. Finally, the rheumatologist would have considered that continuous freedom from symptoms would be likely to depend on maintaining a certain level of drug. In order to achieve that when a weekly dosing interval was increased to dosing every two weeks, the team would expect to approximately double the dose that was used every week (i.e. based on 20mg every week, 40mg would be given every other week). Kempeni 2000 reinforces Prof Edwards' view arising from Kempeni 1999 that 40 mg given every other week would be an obvious dosing regimen to choose.

AbbVie's answer to obviousness in the light of Kempeni 2000

336. AbbVie relies on the same arguments as in relation to Kempeni 1999, which I have not accepted. It also submits that the information concerning DE007 in Kempeni 2000 is extremely sparse, and the skilled person would not take steps or make decisions based upon it until he had seen whether there was any further information available about it.

337. I do not accept this submission, for the following reasons: First, it is not appropriate to read the description of DE007 in Kempeni 2000 in isolation from Kempeni 1999. Kempeni 2000 confirms that subcutaneous administration of 20, 40 and 80 mg would be an appropriate dosage regimen for D2E7, which was already apparent from Kempeni 1999. Secondly, the account of DE007 in Kempeni 2000 would be supplemented by consideration of the abstracts to which I have referred, which provide further information about the DE007 trial. Those abstracts support the conclusion that the data for 20, 40 and 80 mg are not materially different, and all are efficacious doses.

Conclusion in the light of Kempeni 2000

338. Having regard to all the circumstances, I have reached the firm conclusion, based on Kempeni 2000, that the skilled team would have taken forward D2E7 as a subcutaneous treatment. 40mg given every two weeks would have been an obvious dose to choose. The combination of D2E7 and MTX was obvious. The skilled team would have had a high expectation that this regimen, being a variation on the regimen already reported as effective by Kempeni, would be efficacious in the treatment of RA. The skilled team would also have been interested in a two week dosing interval with a higher dose of 80mg and a lower dose of 20mg, to confirm 40mg was at or near the point of plateau of the dose response curve.

339. On this basis, I conclude that the administration of the Claimants' proposed products in the treatment of RA by a dosage regimen of 40 mg once every two weeks by subcutaneous injection was obvious in the light of Kempeni 2000.

The administration of the Claimants' proposed products at a dose 40mg sc every other week for the treatment of psoriasis and psoriatic arthritis – anticipation or obviousness as of 18 July 2003

340. Whilst AbbVie has not admitted anticipation or obviousness as of 18 July 2003, it has not challenged the Claimants' evidence, nor has it presented any positive case. The Claimants have several prior art citations, and also rely upon common general knowledge. I only need to deal with one such citation in order to determine this question.

The prior uses relied on by the Claimants

341. The Claimants rely upon the following:

i) The prior use of adalimumab to treat a patient with moderate to severe chronic plaque psoriasis and PsA ("Patient 1") by Prof J Barker, Skin Therapy Research Unit, St John's Institute of Dermatology, Guy's and St Thomas' Hospital, London, in respect of which adalimumab was administered subcutaneously to the patient at a dose of 40mg every other week, starting in January 2003, to treat the said patient's chronic plaque psoriasis and PsA, such that the chronic plaque psoriasis was treated, thereby making the said use and treatment available to the public;

ii) The prior use of adalimumab to treat a second patient with moderate to severe chronic plaque psoriasis and PsA ("Patient 2") by Dr B Kirkham of the Department of Rheumatology, Guy's and St Thomas' Hospital, London, in respect of which adalimumab was administered subcutaneously to the said patient at a dose of 40mg every other week commencing no later than November 2002 to treat the said patient's chronic plaque psoriasis and PsA, such that the chronic plaque psoriasis was treated, thereby making the said use and treatment available to the public.

iii) The disclosures by the said doctors to the said patients of the said treatment and dosing regimens which they were to receive and which they subsequently did receive as set out in (i) and (ii) above.

342. Having considered the evidence of Prof Barker, and the documents which corroborate his evidence, I find that these prior uses have been established. Accordingly, I find that the administration of the Claimants' proposed products at a dose 40mg sc every other week for the treatment of psoriasis and psoriatic arthritis was anticipated or obvious as of 18 July 2003.

The declaration case

The factual background

The strike out applications

343. In order to evaluate this aspect of the case, a more detailed account of the complex procedural history of these proceedings is required. AbbVie made a series of applications, the effect of which, if successful, would have been to avoid a trial in the United Kingdom. Claim No HP-2015-000053 ("FKB1"), which concerns the 656 patent and the 322 patent, was issued on 29 October 2015. AbbVie applied to strike out parts of that claim, in particular in relation to the *Arrow* declaration. I dismissed that application by a judgment dated 1 March 2016 [2016] EWHC 425 (Pat) ("the FKB1 judgment").

344. On 24 March 2016 SB/Biogen issued Claim No HP-2016-000016 ("S/B") in respect of the same patents as were in issue in FKB1 at that time, and sought a declaratory relief including a declaration in the same form as in FKB1. On 9 May 2016 FKB issued Claim No HP-2016-000025 ("FKB2"), which concerns EP UK 1,737,491 ("the 491 patent"). AbbVie applied to set aside service of, or alternatively to strike out, FKB2. Arnold J dismissed that application by a judgment dated 8 September 2016 [2016] EWHC 2204 ("the FKB2 judgment"). Appeals by AbbVie from the FKB1 and FKB2 judgments were heard on 28 and 29 November, and were dismissed by the Court of Appeal [2017] EWCA Civ 1 ("the FKB Appeal").

345. Having offered certain undertakings (set out below) and having abandoned the patents the subject of the FKB1 and S/B proceedings, AbbVie then applied to strike out the FKB and S/B proceedings for a second time. That application was dismissed by me following a hearing on 9 December 2016; [2016] EWHC 3383 (Pat).

AbbVie's abandonment of patent protection

346. The Particulars of Claim in their original form in FKB1 sought to revoke two granted patents, namely the 656 patent and the 322 patent. The 656 patent claimed the use of adalimumab in the treatment of rheumatoid arthritis by the 40 mg sc eow dosage regimen. The application for the 656 patent was filed on 5 June 2002. It was not granted by the EPO until eleven years later, on 9 June 2013. During the nine month opposition period following grant, fifteen oppositions were submitted. AbbVie eventually filed its observations in response to the oppositions, together with no less than nineteen statements of fact and expert reports, on 22 December 2014. On 24 April 2015 AbbVie requested the grant of a divisional from the 656 patent ("the Fourth Divisional Application"), having previously requested the grant of three other divisionals. Between August and October 2015 various opponents submitted replies to the observations filed on behalf of AbbVie. However, on 4 November 2015, six days after the Claim Form was issued in FKB1, AbbVie wrote to the EPO stating that it no longer approved the text of the granted 656 patent. Accordingly, the EPO revoked the 656 patent on 16 November 2015. The Fourth Divisional Application, which claimed essentially the same subject matter as the 656 patent, was published on 4 November 2015.

347. FKB pleaded these facts by amendment to its Particulars of Claim. It alleged that AbbVie intended to delay the entry of competing Humira biosimilar products by prolonging commercial uncertainty. FKB claimed that the purpose of abandoning the 656 patent was to avoid adjudication on its patentability by the UK court and the Opposition Division, whilst seeking to ensure that the subject matter of the 656 patent was maintained by the Fourth Divisional Application. The object, according to FKB, was to prevent FKB from clearing the way in respect of its FKB327 biosimilar after expiration of the SPC for the basic adalimumab patent.

348. AbbVie disputed that there was any connection between its decision to abandon the 656 patent and the commencement of the UK proceedings by FKB. It claimed that a late insufficiency objection had given rise to its decision. This was strongly disputed by the Claimants in the evidence of their solicitors, who pointed out that the explanation, after so many years of opposition, was not credible. The Claimants wished to cross-examine Ms Rich, who gave evidence about the insufficiency objection, which was relied on by AbbVie in its strike out applications in these proceedings. However, that evidence was withdrawn from the trial by AbbVie, who nonetheless continued to advance the same explanation, based on a letter from its Patent Attorney to the EPO. No witness statement was provided by the Patent Attorney, and the letter was not placed under a Civil Evidence Act Notice. So there was no evidence at trial to support AbbVie's explanation.

349. Whilst, of course, this is no reflection on Ms Rich, I should make it clear that I do not believe AbbVie's explanation for its decision to abandon the 656 patent. I do not consider that it was credible, for the reasons explained by Mr Inman in his evidence. Knowing that it was disputed, AbbVie took steps to ensure that it could not be tested in cross-examination. Furthermore, subsequent events have confirmed, in my judgment, that AbbVie has abandoned all relevant UK patent protection in order to avoid scrutiny by the UK Court, and to prolong commercial uncertainty as to the validity of those patents. The claim that the 656 patent was abandoned because of a late insufficiency objection needs to be considered in this context.

350. It is now necessary to explain the fate of the Fourth Divisional Application. The Fourth Divisional Application was granted on 16 November 2016 as the 044 patent. From the beginning of October 2016, the parties were proceeding on the basis that the 044 patent would be granted in time for the FKB1 trial, and AbbVie confirmed this in correspondence. Accordingly, FKB and SB/Biogen produced pleadings to challenge the validity of the 044 patent. The pleadings also sought revocation of the 322 patent, which was to be considered at the FKB1 trial. Both parties served extensive expert evidence on 8 November 2016, each side relying on three expert reports, addressing the issues raised by the 044 and 322 patents and the *Arrow* declarations.

351. On 18 October 2016 AbbVie's solicitors wrote to the Claimants' solicitors stating that:

> "there are no patent applications in the same family as, or claiming the same priority date as, EP 656 that relate to the treatment of rheumatoid arthritis by the administration of 40

> mg every other week of adalimumab by subcutaneous injection as monotherapy"

352. FKB's solicitors replied by letter dated 21 October 2016, pointing out that it was open to AbbVie to file further divisionals, and asking for confirmation that AbbVie would not file applications covering the same subject matter. This confirmation was not provided.

353. On 15 November 2016, without any explanation, AbbVie de-designated the UK from the 044 patent, and disapproved the text of the 322 patent, leading to its revocation. Furthermore, AbbVie indicated that it would submit the 491 patent, the subject of the FKB2 proceedings, to revocation in respect of the UK. However, the Claimants' advisers discovered that, at some point prior to this letter, AbbVie had filed a new divisional application to the 044 patent ("the Fifth Divisional Application"). The existence of the Fifth Divisional Application was not mentioned in the letter of 15 November 2016; Gilbert (3) [29] – [33].

354. On 9 December 2016 AbbVie offered the following undertakings. I will consider their effect later in this judgment.

> "AND UPON the Defendant undertaking (on behalf of itself and its affiliates):
>
> (1) not to obtain patent protection in the UK that would be infringed by importing into the UK, making, offering to sell or dispose of, selling and/or disposing of and/or keeping for such sale or disposal the Claimant's products containing its biosimilar monoclonal antibody to the antibody adalimumab (Humira) as a result of such products being:
>
> (a) for the treatment of rheumatoid arthritis by the administration by subcutaneous injection of 40mg every other week of adalimumab (whether or not co-administered with methotrexate) where such patent claims a priority date of 8th June 2001 or later;
>
> (b) for the treatment of rheumatoid arthritis by the administration by subcutaneous injection of 40mg every week of adalimumab as a monotherapy where such patent claims a priority date of 8th June 2001 or later;
>
> (c) for the treatment of psoriasis and/or psoriatic arthritis by the administration by subcutaneous injection of 40mg every other week of adalimumab (whether as an initial or continuing dosing regimen) where such patent claims a priority date of 18th July 2003 or later; or
>
> (d) for the treatment of psoriasis by the administration by subcutaneous injection of 40mg every week of adalimumab

> (whether as an initial or continuing dosing regimen) where such patent claims a priority date of 18th July 2003 or later;
>
> (e) for the treatment of any indication by the administration by subcutaneous injection of 40mg adalimumab weekly or every other week (where such patent claims a priority date of 8th June 2001 or later);
>
> (2) not to assign any GB or European patent protection in the UK corresponding to that referred to in undertaking (1) above in respect of such patent application;
>
> (3) not to designate the UK in or (as the case may be) to de-designate the UK from any patent application which is a direct or indirect divisional of EP 1 406 656 or EP 2 012 824, including, for the avoidance of doubt, EP 16198524.7 and EP 2 666 478 A;
>
> (4) not without the permission of the Court to threaten, commence or pursue against the Claimant (or its customers or agents) any action for infringement of a UK patent in respect of any act to which undertaking (1) above pertains.
>
> For the avoidance of doubt, the effect of the said undertakings is that the Defendant and its affiliates will not obtain UK patent claims that contain, as an integer, the use by subcutaneous injection of 40 mg adalimumab weekly or every other week (where such patent claims a priority date of 8th June 2001 or later)."

355. Following central revocation of the 322 patent, by a letter dated 22 December 2016, AbbVie asserted that there was no European patent which had, "as an integer of its claims", the treatment of psoriasis and/or psoriatic arthritis by the administration by subcutaneous injection of 40mg every other week of adalimumab (whether as an initial or continuing dosage regimen). It asserted that there were no extant members of that patent family and no divisionals could be filed.

356. The Claimants point out that AbbVie has served no evidence to support its assertion that it is impossible for any European patent rights to arise out of the 322 patent family, or indeed other families which enable the same subject matter to be claimed. Not only is there no evidence to support this assertion, but also there is a positive reason not to accept it. The Claimants rely upon a pending EP application (X3) with examples reporting clinical trials of the 40 mg sc eow regimen (plus a loading dose) for psoriasis, from which a further psoriasis divisional could be derived. I accept the Claimants' submissions on this issue. In the absence of any evidence from AbbVie, I am not prepared to find that it is impossible for any European patent rights to arise out of the 322 patent family, or other families which enable the same subject matter to be claimed. The filing of the Fifth Divisional Application shortly prior to withdrawal of the GB designation from the 044 patent lends further support to the Claimants'

submission. However, the effect of the undertaking provided by AbbVie may be that such further patent rights cannot extend to the UK, an issue to which I refer below.

357. The Claimants contend that all this is consistent with AbbVie's well-established strategy of dragging out proceedings for as long as possible, causing maximum expense and inconvenience to its opponents, and then throwing in the towel just before its patents are scrutinised by the court or tribunal, whilst covering the same subject matter with further divisionals.

358. AbbVie's answer is that none of this matters. Since it is submitting to revocation of all EP (UK) patents concerning the dosage regimens in issue in these proceedings, and giving undertakings in respect of future applications, there can be no useful purpose to the grant of declaratory relief..

AbbVie's statements concerning its Humira patent portfolio

359. The Claimants rely upon transcripts of statements by AbbVie's Chief Executive Officer, Mr Gonzalez, where he expressed AbbVie's intention to seek injunctive relief to prevent "at-risk" launches of products which are biosimilar to Humira. As I set out in the FKB1 judgment, during 2015, Mr Gonzalez expressed AbbVie's intention to seek injunctive relief to prevent "at-risk" launches of products which are biosimilar to Humira. Mr Inman stated at 5.41 that "FKB therefore takes AbbVie's statements that it "intends to enforce [its IP] vigorously" and that it will "seek injunctive relief" to apply equally to its European Humira patent portfolio." This was not challenged in reply evidence served on behalf of AbbVie. Given the commercial importance of Humira, it would be surprising if AbbVie did not intend to enforce patent rights which it may be granted in the future by seeking injunctive relief.

360. Since March 2015 Mr Gonzalez has made similar statements, which the Claimants have pleaded by amendment. In the "Q2 2016" earnings conference call Mr Gonzalez said:

> "Back in October, we outlined in detail the extensive portfolio of IP that we have for HUMIRA and our confidence in that IP and it goes beyond any one single patent. And I can tell you that we remain confident in that IP portfolio and we've made it very clear that we intend to vigorously defend all of our IP against anyone that potentially infringes it.
>
> …
>
> I think we have a strategy that we have developed that we will put in place at the point at which we see biosimilar competition in any market around the world. We will obviously implement that strategy outside the US potentially earlier, in an earlier timeframe."

361. In the Q3 2016 call in October 2016, Mr Gonzalez said:

> "Yeah, I mean, based on the long-term expectations, as we've communicated to the market before, we don't anticipate biosimilar competition in the U.S. market for quite some time. And so I think we have a strategy that we have developed that we will put in place at the point at which we see biosimilar competition in any market around the world. We'll obviously implement that strategy outside the U.S. potentially earlier, in an earlier timeframe."

362. The Claimants submit that Mr Gonzalez' comments, and AbbVie's strategy to counter biosimilar competition to which he refers, is not jurisdiction specific, but will be deployed in "any market around the world".

363. Mr Tappin took me through certain of the transcripts, in order to give context to the statements. He submitted that in Q3 2015 Mr Gonzalez had drawn a distinction between the position in the US and the position elsewhere, including Europe. He submitted that his statements concerning vigorous enforcement of the Humira patent estate related to the US, and not to Europe. He contended that the same was true in relation to the Q2 2016 earnings call. In relation to the Q3 2016 earnings call, Mr Tappin submitted that Mr Gonzalez had been speaking extensively about commercial matters including price and formulary access. Therefore, his answers were concerned with pricing strategy once there was biosimilar competition on the market.

364. In my view, there is some force in this submission, and I have looked at all the statements in the context of the transcripts as a whole. However, the first time that there was any suggestion by AbbVie that threats of enforcement were limited to the United States was in its closing at trial, even though Mr Gonzalez' statements had been relied upon in each of the strike out hearings. I also consider it material that AbbVie called no evidence, whether from Mr Gonzalez or anyone else, to challenge the assertion of worldwide threats. Furthermore, I do not accept that all of the statements can be regarded as limited to the US, or as relating to commercial issues. I consider that Mr Gonzalez clearly represented that AbbVie would make every effort to enforce its patent estate against biosimilar competition anywhere in the world.

Legal principles

The discretion to grant declarations

365. In *Messier-Dowty v Sabena* [2001] 1 All E.R. 275 Lord Woolf MR explained at [41] that the approach to the grant of declarations is pragmatic, and a matter of discretion rather than jurisdiction. He stated that the use of negative declarations should be rejected where it would serve no useful purpose. Negative declarations are unusual and caution should be exercised when extending the circumstances in which they are granted. On the other hand, where a negative declaration would help to ensure that the aims of justice are achieved "the courts should not be reluctant to grant such declarations. They can and do assist in achieving justice."

366. In *Financial Services Authority v Rourke* [2002] C.P. Rep. 14 Neuberger J stated that the power to make declarations was unfettered, and that the court had to consider

whether, in all the circumstances, it was appropriate to make such an order. He held that when considering whether to grant a declaration, the court should take into account "justice to the claimant, justice to the defendant, whether the declaration would serve a useful purpose and whether there are any other special reasons why or why not the court should grant the declaration."

367. Certain other authorities shed light on the meaning of useful purpose. A declaration that has no useful purpose is commercially pointless. This was explained, with characteristic clarity, by Pumfrey J in *Nokia Corp v Interdigital Technology Corp*. [2007] EWHC 3077 (Pat) at [42]. His judgment was upheld on appeal.

> "42 … the principal factor affecting the exercise of the court's discretion, apart from such matters as the sufficiency of the description of the device or system to which the invention is said to be inessential, is the utility of the negative declaration sought. Would the declaration if granted be the legal equivalent of shouting in an empty room, or is there some point in it?"

368. It is well established that the attainment of commercial certainty in patent cases can be a useful purpose, and it may be in the interests of justice to grant a declaration to dispel commercial uncertainty. This was emphasised by Kitchin J in *Arrow Generics v Merck & Co Ltd* [2007] EWHC 1900 (Pat)) at [58]:

> "there is a public interest in commercial certainty in patent matters as in any others. Business needs to know where it stands. I believe this court should assist in providing that certainty where it properly can"

369. The same point has been made more recently by the Court of Appeal in the context of whether to stay UK proceedings where there are co-pending proceedings in the EPO. In *IPCOM v HTC* [2013] EWCA Civ 1496 Floyd LJ stated at [8] that:

> "8. The Patents Court judge is entitled to refuse a stay of the national proceedings where the evidence is that some commercial certainty would be achieved at a considerably earlier date in the case of the UK proceedings than in the EPO. It is true that it will not be possible to attain certainty everywhere until the EPO proceedings are finally resolved, but some certainty, sooner rather than later, and somewhere, such as in the UK, rather than nowhere, is, in general, preferable to continuing uncertainty everywhere."

370. In the FKB Appeal Judgment, the Court of Appeal rejected the submission that *Arrow* was wrongly decided, and made clear that there was jurisdiction to grant such declarations. The issue is whether a sufficient case can be made out for the exercise of the court's discretion, in accordance with established principles, and having regard to the existence of the statutory remedy of revocation provided for by section 74 of the Patents Act 1977. Floyd LJ said at [93] that:

> "93 The eventual existence of the statutory remedy of revocation is, in our judgment, of relevance to the question of whether a declaration should be granted in the exercise of the court's discretion. A claimant cannot seek an Arrow declaration simply because it would like to know whether a patent application in the course of prosecution will result in a valid patent. The course envisaged by the statute is that he should wait and see what, if any, patent is granted. The statutory remedy does not constitute a bar in principle to the granting of declaratory relief in appropriate cases, however. Where, for example, it appears that the statutory remedy is being frustrated by shielding subject matter from scrutiny in the national court, it should be open to the court to intervene. Just as in Nokia , the statutory remedy does not provide, in practical terms, the relief which the claimant needs."

371. As to the principles on which the discretion should be exercised, Floyd LJ said at [99] – [100] that:

> "99 Given that a discretionary power exists, it is for the Patents Court to develop the principles for its exercise in more detail. It will be apparent from the above, however, that we consider an important factor to be borne in mind in the exercise of the discretion is the existence of the statutory proceedings for revocation, which should be regarded as the normal vehicle for obtaining any desired findings of invalidity.
>
> 100 In submitting, as he does, that this is a case where no judge could exercise the discretion to grant an Arrow declaration Mr Hobbs faced, as we think he recognised, an uphill task. It seems to us that the pleaded facts in both cases are at least open to the interpretation that AbbVie are deliberately trying to shield the claims of their patents from scrutiny in the EPO and in the national court. Had the patents not been voluntarily de-designated or revoked, FKB would have had the opportunity to seek findings of invalidity of granted patents in the usual way. Those findings would have gone a long way to establishing its freedom to operate before launch. Because of the way AbbVie have appeared to act, there is a case for the court to intervene by way of declaration to provide FKB with a measure of useful commercial certainty."

"Spin-Off" value of judgments

372. The Claimants emphasise the assistance that judgments of the Patents Court can provide to other courts in EPC contracting states who are required to consider the same issues. They rely on the judgment of Arnold J in *TNS v Nielsen* [2009] EWHC 1160 (Pat):

> "In my judgment, those authorities demonstrate that it is perfectly legitimate for the claimant to seek to obtain a judgment of this Court on the validity of the patent in suit in the hope that it will lead to a settlement of the dispute between the parties throughout Europe. Nor, in my judgment, would it be in any way illegitimate for the claimant, absent such a settlement being achieved, to seek to rely upon the judgment of the English court in proceedings before the courts of other contracting states or the European Patent Office. It is commonplace for parties litigating on the same European patent in a number of contracting states to put before the courts of one contracting state decisions arrived at in one or more other contracting states."

373. The Claimants also rely upon the statement of Jacob LJ in *Grimme Landmaschinenfabrik GmbH & Co KG v Scott (t/a Scotts Potato Machinery* [2010] EWCA (Civ) 1110 at [80]:

> "Broadly speaking we think the principle in our courts – and indeed that in the courts of other member states – should be to try to follow the reasoning of an important decision in another country. Only if the court of one state is convinced that the reasoning of the court in another member state is erroneous should it depart from a point that has been authoritatively decided there. Increasingly that has become the practice in a number of countries, particularly in the important patent countries of France, Germany, Holland and England and Wales. Nowadays we refer to each other's decisions with a frequency which would have been hardly imaginable even years ago. And we do try to be consistent where possible."

374. I accept that the spin-off value of a judgment in a contracting state can be very valuable, and it is legitimate for parties to rely upon such judgments in other contracting states. However, it is important not to extend this principle too far. Statements as to the spin-off value of UK judgments have been made in the context of applications to stay pending resolution of EPO oppositions, or of applications to expedite trials. Those cases are very different from the present. It is also important to guard against forum shopping, where a declaration from the UK Court is sought in cases which have no connection with this jurisdiction.

375. This is illustrated by the judgment of the Court of Appeal in *Dow Jones v Jameel* [2005] EWCA Civ 75. The on-line version of the Wall Street Journal had published an article linking the Claimant to the funding of al Qaeda. The Claimant brought libel proceedings in the United Kingdom even though very few United Kingdom residents had seen the article. One of his objects was to seek a judgment which would vindicate him in respect of the global publication. When considering the question of vindication, the Court of Appeal at [65] referred to the judgment of Lord Hoffman in the *Berezovsky v Michaels* [2001] 1 WLR 1004:

> "The plaintiffs are forum shoppers in the most literal sense. They have weighed up the advantages to them of the various jurisdictions that might be available and decided that England is the best place in which to vindicate their international reputations. They want English law, English judicial integrity and the international publicity which would attend success in an English libel action.
>
> …
>
> My Lords, I would not deny that in some respects an English court would be admirably suitable for this purpose. But that does not mean that we should always put ourselves forward as the most appropriate forum in which any foreign publisher who has distributed copies in this country, or whose publications have been downloaded here from the Internet, can be required to answer the complaint of any public figure with an international reputation, however little the dispute has to do with England. In Airbus Industrie G.I.E. v Patel [1991] 1 AC 119 your Lordships' House declined the role of "international policeman" in adjudicating upon jurisdictional disputes between foreign countries. Likewise in this case, the judge was in my view entitled to decide that the English court should not be an international libel tribunal for a dispute between foreigners which had no connection with this country."

376. The Court of Appeal in *Jameel* concluded at [66]:

> "So far as concerns the issue currently under consideration there is no conflict between the view of Lord Hoffmann and the view of the majority. This action falls to be considered as relating exclusively to an independent tort, or series of torts, in this country. It is thus not legitimate for the claimant to seek to justify the pursuit of these proceedings by praying in aid the effect that they may have in vindicating him in relation to the wide publication."

377. This (amongst other authorities relied on by AbbVie) shows that, when considering whether to grant the declaration in the present case, I am concerned with whether it will serve a useful purpose in the United Kingdom. A declaration which is sought solely for the benefit of foreign courts will rarely be justified, as was emphasised by Floyd LJ in the FKB Appeal Judgment.

> "95 We are not persuaded that declarations in the *Arrow* form will open any floodgates. The *Arrow* decision is now of some age, and has not resulted in many such cases being brought. The circumstances in which such declarations will be justified, will, we would have thought, be uncommon. Mr Hobbs'

> example of a business problem in Romania would be unlikely to justify the grant of a declaration by the English court."

Evidence in the present case

378. AbbVie called no evidence in relation to useful purpose, or in relation to any other of the factors that may be relevant to the discretion to grant the declarations. The Claimants relied at trial upon the evidence of Mr Paul Inman, the solicitor with conduct of this matter on behalf of FKB, and Dr Penny Gilbert, the solicitor with conduct of this matter on behalf of SB/Biogen, whose witness statements had been served in answer to the strike out applications. Mr Inman and Dr Gilbert were due to be cross-examined on behalf of AbbVie. However, during the second week of the trial, on the day before this cross-examination was due to take place, AbbVie's representatives indicated that it did not intend to cross-examine either of them. These witness statements therefore stand unchallenged.

Would the declarations sought serve a useful purpose?

AbbVie's case

(i) The way is now clear in respect of dosage regimens in the UK

379. AbbVie submits that the question of whether a declaration would serve a useful purpose is to be assessed on the facts as they exist at the time of the trial, as of when AbbVie neither has, nor can obtain, any relevant rights in the UK claiming a priority date of 8 June 2001 or later. The fact that at an earlier point in time AbbVie had or could obtain such rights is irrelevant.

380. AbbVie contends that it has now taken steps leading to revocation of all patents in issue in these proceedings and has given clear and unambiguous undertakings to the Court to ensure that there will never be UK patent claims claiming a priority date of 8 June 2001 or later that contain, as an integer, the dosing regimens specified in the declarations sought by the Claimants. Therefore, there is no risk that patent protection in the United Kingdom will be infringed by the Claimants' products as a result of their use in accordance with the dosage regimens in issue. The Claimants have cleared the way of patent protection in the United Kingdom, and so have achieved the utility and commercial purpose of the *Arrow* declarations. The purpose of the declarations was to provide the Claimants with a "Gillette defence" to complaints of acts committed in the United Kingdom, on the basis that if there is infringement of any existing or future patent which claims the specified dosage regimen, then such patents must be invalid. This has now been achieved.

381. AbbVie relies upon [43] of the FKB1 judgment where I said:

> "the existence of the divisional applications gives rise to the need and justification for seeking declaratory relief. AbbVie could withdraw the "GB" designations of the divisional applications or acknowledge that it can have no claim under them in this country in respect of a product having the specified characteristics of FKB's product. If it did so then the

> commercial purpose of the declarations sought would fall away"

382. AbbVie submits that it has taken this course and therefore there is no commercial purpose in pursuing the case to trial. AbbVie points out that it is not the function of the UK Patents Court to act as an advisory body for other courts around Europe, and it would be wrong to make a declaration solely for that purpose. It points out that *Arrow* declarations must be limited to the United Kingdom as a matter of comity and respect for decision-making in other jurisdictions, and because of Articles 24 and 27 of the recast Brussels Regulation 1215/2012. These declarations are so limited, but this shows that they cannot have any effect outside of the United Kingdom.

(ii) AbbVie did not need to give an acknowledgement or submit to judgment

383. AbbVie submits that where the way has already been cleared in the United Kingdom in respect of the dosage regimens in issue there is no reason why it should give an acknowledgement in terms of the declaration, nor submit to the making of a declaration. It argues that its refusal to do so is understandable, since it fundamentally disagrees with the factual premise of the declarations, for the reasons advanced as part of its technical case.

(iii) AbbVie did not need to call any evidence in relation to useful purpose

384. AbbVie contends that the Claimants' evidence is defective and fails to establish any useful purpose. AbbVie submits that its subjective intentions as to why it abandoned UK patent protection are irrelevant, and the only question is the objective result of its actions. AbbVie argues that it could not have adduced evidence as to its patent strategy, and the thinking and intentions behind its actions, without waiving privilege. For example, if it had adduced evidence as to its subjective intention in abandoning the 656 patent, it would have to have waived privilege in respect of its internal analyses of the strengths and weaknesses of the objections in the EPO opposition proceedings. No adverse inferences can be drawn against a litigant on the basis that it has chosen to maintain privilege; *Oxford Gene Technology v Affymetrix* (No 2) [2001] RPC 18 at [21] and [56].

(iv) AbbVie did not need to cross-examine Mr Inman or Dr Gilbert

385. AbbVie submits that this evidence was immaterial, fails to establish the propositions advanced by the Claimants and was in parts inadmissible.

Assessment

386. I do not accept AbbVie's submissions, and I accept the Claimants' case on this issue, to the extent set out below. If, as AbbVie submits, the declarations have no useful purpose, and the steps that they have taken have the same effect in achieving commercial certainty, there is no coherent explanation as to why it refuses to submit to judgment, or alternatively to give an acknowledgement in the same form as the declarations. The suggestion that AbbVie resists the declarations because it does not accept that the relevant dosing regimens were anticipated or obvious does not withstand examination, and has not been put forward in evidence. If that were the

case, AbbVie would not have abandoned its UK patent protection. Had it maintained that protection, and won the trial, it would have been able to stop the launch of the Claimants' biosimilars.

387. In my judgment, AbbVie would not have invested the considerable resources that this trial has required unless there was a good commercial reason to resist the declarations. In the absence of any alternative explanation in evidence, I believe that the declarations will be more damaging to AbbVie's strategy in relation to its Humira patent portfolio than the complex set of undertakings and abandonment of UK patent protection that it has chosen to provide.

388. I also note that by paragraph 6D of FKB's Re-Amended Particulars of Claim, and by paragraph 7C of SB/Biogen's Re-Amended Particulars of Claim, The Claimants allege that the object and cumulative consequence of AbbVie's conduct is intended to delay the entry of competing biosimilars, and AbbVie has sought to achieve this by prolonging commercial uncertainty by a series of acts of abandonment of protection, whilst re-filing divisionals for essentially the same subject matter. This puts into issue AbbVie's intentions, which I do not accept are irrelevant, on the basis of the pleaded issues. However, even if I were to consider only the objective effect of AbbVie's conduct, my conclusions would be no different. I consider that the intention and the objective effect is to shield its patent portfolio from examination of validity whilst continuing to file further divisionals and to threaten infringement proceedings against biosimilars, wherever they may be launched.

389. I do not accept that AbbVie was unable to advance an explanation for its conduct in evidence, without waiving privilege. At the strike out applications, and during this trial, AbbVie advanced a positive case as to why it had abandoned the 656 patent. It relied on the evidence of Ms Rich concerning a late insufficiency objection, which was carefully drafted to avoid any waiver of privilege. There was no suggestion by the Claimants that privilege had been waived as a result of this evidence. AbbVie continued to advance this explanation in its written closing on the declarations at [129] – [133], although by this stage it had made clear that it would not be calling Ms Rich (or anyone else) to give evidence on this issue at trial.

390. I accept that an *Arrow* declaration provides a Gillette defence to allegations of infringement in the United Kingdom, and any such declaration must be limited to the United Kingdom. However, I have to consider the Claimants' case as it is now pleaded and supported by evidence, and ask whether those allegations are justified, and constitute a useful purpose. The circumstances now relied on are not the same as in *Arrow*, nor are they the same as were originally pleaded. Describing these declarations as *Arrow* declarations is a potentially misleading shorthand, as the purpose of the declarations is different.

391. AbbVie is, of course, entitled to rely upon passages in the FKB1 judgment concerning the effect of de-designation of UK patent protection and appropriate acknowledgements. However, those statements were based on the pleadings and evidence that were before the Court at the time. I am now faced with different pleadings, supported by evidence, which rely on additional facts in support of additional claims of the utility of the declarations. The Claimants are entitled to have

their claim considered on the basis of those pleadings and evidence, since AbbVie has radically shifted its position since the FKB1 judgment.

392. I do not accept that the history of these proceedings is irrelevant. The Claimants have, on a number of occasions, tried to exercise their statutory right to seek revocation of AbbVie's UK patents. AbbVie has abandoned its UK patent protection shortly before trial, and has a long record of similar conduct. This is quite different from a case which has never had any connection with the United Kingdom, and is brought purely to influence foreign courts.

393. In my view, AbbVie needed to cross-examine Mr Inman and Dr Gilbert if it wished to challenge their evidence. I do not accept that their evidence, which I consider below, was immaterial or lacking in clarity. During AbbVie's closing, it was alleged for the first time that aspects of Mr Inman and Dr Gilbert's evidence were inadmissible as they concerned the effect of inclusion of a judgment or declaration in a German protective brief. The admissibility objection was far too late. If it was a part of AbbVie's case, it should have been raised well before the trial, rather than after the evidence had been admitted and the Claimants had closed their case. Furthermore, I consider that solicitors with very extensive experience of European patent litigation are entitled to give such evidence. If it was to be said that they were unable to do so from their own knowledge, this should have been put to them in cross examination.

394. I consider that the grant of a declaration would serve a useful purpose, for the following reasons. First, commercial certainty. Mr Inman and Dr Gilbert suggested in their evidence that the reason why AbbVie had abandoned its UK patents was to shield them from the scrutiny of the UK Courts. They claimed that AbbVie continued to resist the declarations precisely because they would serve a useful purpose, namely to provide the Claimants with adequate certainty as regards the intended launch of their biosimilar adalimumab products; see for example Gilbert (3) [33].

395. I consider that these claims are justified. I have set out above the extensive history of the proceedings in the EPO and the UK, which shows, in my judgment, that AbbVie has made every effort to shield the claims of its patents from scrutiny in the EPO and in the UK Court. Had the patents not been voluntarily de-designated or revoked, the Claimants would have had the opportunity to seek findings of invalidity of the granted patents pursuant to section 74 of the Patents Act 1977 and thereby to dispel any uncertainty. AbbVie's conduct has been designed to prevent that from happening, and has had that objective effect.

396. In my judgment, AbbVie has consistently adopted a policy of publicly expressing its confidence in its Humira patent portfolio, and its intention to enforce it against competition from biosimilars, whilst at the same time shielding patents within the portfolio from scrutiny by the court. When patent protection has been abandoned by AbbVie, another sub-divisional has been applied for, thereby perpetuating commercial uncertainty.

397. I have also found that AbbVie has made threats that it will enforce its patents against biosimilar competition anywhere in the world. The declarations will serve a useful

purpose of dispelling commercial uncertainty in the UK (and European) market, which those threats have created.

398. As against this, I need to consider the effect of the undertakings offered by AbbVie. They are certainly not a masterpiece of drafting, which may be explained by the fact that they were redrafted on at least four occasions, in answer to objections by the Claimants. The undertakings are complicated and very long. They do not refer to anticipation or obviousness, and they do not acknowledge that the Claimants' products were anticipated or obvious at the priority date(s). AbbVie undertakes not to obtain patent protection in the UK that would be infringed by certain dosage regimens, which is difficult to follow, as it begs the question as to whether such patent protection will be applied for, and if so, why it would not be infringed. This is clarified by the avoidance of doubt provision at the end of the undertaking, but none of this is easy to understand, particularly for companies seeking to do business with the Claimants in respect of their biosimilars. Such companies would need to understand why the undertaking is limited to patent claims which claim a priority date of 8 June 2001 or later and would also need to understand, and believe, that AbbVie has abandoned all existing patent protection to these dosage regimens in the UK.

399. I have carefully considered the effect of the undertakings, including the avoidance of doubt provision, which does prevent AbbVie from obtaining UK patent claims in the future which claim the specified dosage regimens (where such patent claims a priority date of 8 June 2001 or later). Nonetheless I accept the Claimants' submission that the declarations provide clarity for third parties in the United Kingdom. Such clarity is necessary, given AbbVie's conduct to date, and is not provided by AbbVie's undertakings.

400. Furthermore, I need to consider the consequences if I were to refuse to grant the declarations, having decided that the Claimants should succeed in their technical case. In those circumstances the Claimants will have failed to obtain the relief which they sought, in spite of winning the trial. That, in my judgment, would be a recipe for uncertainty, which the undertakings would be unlikely to remedy.

401. I also consider that the declaration would serve a useful purpose in protecting the Claimants' supply chain for the UK market. At [2.8(a) – (b)] of his eleventh Statement, Mr Inman expressed concern as to the "chilling effect" in the market, in the absence of a declaration, in that manufacturers of products are likely to find it more difficult to enter into an agreement with a prospective EU marketing partner, when despite the UK being patent free, the rest of the EU remained subject to the threat of potential patent litigation. He explained that, as a practical matter, due to the international nature of the industry, most biosimilar manufacturers will be unable to confine their manufacture and supply chain to within the UK, so the UK market may not be able to be exploited without being at risk of AbbVie's patents in other jurisdictions.

402. At [2.a] of his twelfth statement, Mr Inman provided more detail to this evidence. He stated that:

> "Mr Nomura, CEO of FKB, has informed me that FKB's plans for launching FKB-327 will involve certain aspects of manufacture and supply taking place within Europe (outside of the UK). In particular, FKB's current intention is that its European supply chain will involve at least three unconnected third party suppliers and activities in at least two other jurisdictions."

403. On the basis of this evidence, the Claimants submit that the UK market will be directly affected by continuing uncertainty in the absence of a declaration, as it will be unable to confine its manufacture and supply chain to within the UK, so the UK market may not be able to be exploited without being at risk of AbbVie's patents in other jurisdictions.

404. Dr Gilbert explained in her fourth statement at [7] – [9] that if AbbVie were to commence proceedings for infringement of those patents which it has de-designated for the UK in other European jurisdictions, then it is foreseeable that this will have an effect on the supply of SB/Biogen's biosimilar to the UK market. She stated that once manufactured or imported into the EU, a pharmaceutical product may be transferred to other countries for QA release in accordance with EMA requirements, and may be transferred elsewhere for filling into vials, packaging and labelling before being stored at a central distribution hub. An injunction obtained at any of these locations could disrupt the European supply chain, including supply to the UK market. Dr Gilbert has been informed that SB/Biogen's plans for launching SB5 in the UK will involve such a European supply chain.

405. This evidence goes beyond spin-off value to assist the Claimants' products to be launched in other jurisdictions. It explains how the grant of a declaration will make injunctive relief in other jurisdictions less likely, and why this will be of direct benefit to the UK market.

406. I accept the Claimants' submissions. AbbVie did not rely on any evidence in answer to the evidence of Mr Inman and Dr Gilbert, and chose not to explore it in cross-examination. Mr Gonzalez's threats of worldwide litigation are intended to have, and are likely to have had, a chilling effect on competition from biosimilars, including on third-party suppliers. That is likely to impede the Claimants' ability to market successfully their products in the United Kingdom. I consider that the grant of declarations, in these circumstances, will serve a useful purpose.

407. I also consider that the promotion of settlement is relevant. At [2.6] of his eleventh statement, Mr Inman stated that a useful purpose of the declaration would be that it was likely to promote settlement. The Claimants submit that a declaration that a material part of AbbVie's portfolio cannot be enforced in the UK would change the parties' negotiation leverage and promote settlement on fairer terms. This, it is said, is of direct benefit in the UK (as well as the rest of the world) as AbbVie may seek to enforce other patents in the UK (for example formulation patents).

408. In the course of its submissions, AbbVie denied that there is a possibility of settlement, and claimed that a declaration would make no difference. However, it has

put in no evidence on the issue and has not sought to explore Mr Inman's evidence in cross examination.

409. In my view, there is some weight to this point. It is reasonably foreseeable that the grant of the declarations will promote a settlement on a European or even a worldwide basis, in that it changes the parties' negotiating positions. AbbVie would need to take account of the fact that the Court has declared that it cannot prevent the marketing of the Claimants' products in spite of AbbVie's public statements to the contrary, which have extended to Europe in general.

410. The circumstances of this case are most unusual, given AbbVie's strategy which I have outlined above. I consider that the promotion of settlement, in combination with the other factors relied on by the Claimants, provides a useful purpose for granting the declarations.

411. I now turn to the question of spin-off value. The Claimants submit that the declarations will be influential in other European Courts and tribunals, and will make it more difficult for AbbVie to obtain preliminary injunctions, particularly in jurisdictions where validity cannot be challenged whilst patents are under opposition in the EPO.

412. I accept that the spin-off value of a judgment in a contracting state can be very valuable, and it is legitimate for parties to rely upon such judgments in other contracting states. However, on reflection and having regard to the legal principles which I have set out above, I have not taken this into account other than to the extent that this issue may have an impact on the UK market (see Gilbert (4) [7] - [9]).

Justice to the Claimants

413. The Claimants contend that yet again AbbVie has abandoned its patent protection after a great deal of evidence has been served, and at a very late stage in the proceedings. They submit that it will be just to grant the declaration to minimise the risk of repetition of this conduct, which is designed to shield AbbVie's patent portfolio from scrutiny.

414. I have concluded that the grant of the declarations will achieve one or more useful purposes. There has been a contested trial in which AbbVie has sought to resist the relief claimed and in which the Claimants have succeeded. In those circumstances, it is just to the Claimants to grant such declarations.

Justice to the Defendant

415. For the same reasons, there is no injustice to AbbVie in granting the declarations. Having concluded that the dosage regimens of the Claimants' products were anticipated or obvious at the priority dates, and that the declarations will serve a useful purpose, I do not consider that the grant of this relief can be resisted.

Special reasons for or against the grant of the declarations

416. I consider that, on the most unusual facts of this case, there are special reasons which support the grant of the declarations. These include AbbVie's conduct of threatening infringement whilst abandoning proceedings at the last moment (in order to shield its patent portfolio from scrutiny); the amount of money at stake for the Claimants in terms of investment in clinical trials and potential damages if they launch at risk; and the need for commercial certainty, having regard to AbbVie's threats to sue for infringement throughout the world.

Conclusion

417. I consider that it is in the interests of justice to grant the declarations sought, in the unusual circumstances of this case.

Summary of conclusions

418. I conclude that:

i) AbbVie has proved that, at the date of filing of the PCT Application on 5 June 2002, Abbott Bermuda was "successor in title" to the invention the subject of US 961. Therefore, the 656 patent was entitled to its claimed priority date of 8 June 2001

ii) The administration of the Claimants' proposed products in the treatment of RA by a dosage regimen of 40 mg once every two weeks by subcutaneous injection was obvious as of 8 June 2001 in the light of Kempeni 1999.

iii) Further or alternatively, the administration of the Claimants' proposed products in the treatment of RA by a dosage regimen of 40 mg once every two weeks by subcutaneous injection was obvious as of 8 June 2001 in the light of Kempeni 2000.

iv) The administration of the Claimants' proposed products at a dose 40mg sc every other week for the treatment of psoriasis and psoriatic arthritis was anticipated or obvious as of 18 July 2003.

Annex 1

Agreed chronology of events in relation to entitlement to priority

Date	Event	Document bundle reference
July 1987	Dr Kempeni commenced employment with Knoll AG	
19 May 1993	Dr Fischkoff signed EISA	[F2.C/33]
June 1993	Dr Fischkoff commenced employment with KPC	
5 May 1998	Dr Weiss signed EISA and commenced employment with KPC	[F2.C/34]
25 August 1999	Dr Weiss ended employment with KPC	
In or around 1999 or 2000	Invention made by Dr Fischkoff, Dr Weiss and Dr Kempeni	
14 Dec 2000	Abbott Laboratories agreed to buy BASF AG's pharmaceutical business - **Purchase Agreement**	[F2.A/3]
1 March 2001	Abbott Laboratories designated Abbott Deutschland Holding GmbH to hold shares and patent rights acquired under the Purchase Agreement – Management Agreement	[F2.B/11]
2 March 2001	Closing of Purchase Agreement Patents assigned from BASF AG to Abbott Deutschland Holding GmbH – **Patent and Patent Application Assignment and Agreement**	[F2.B/17]
9 March 2001	Knoll AG transformed into a new legal form known as Knoll GmbH	[F2.C/38]
31 March 2001	Dr Kempeni ended employment with Knoll AG	
8 June 2001	**The priority application (US961)** was filed in the names of Dr Kempeni, Dr Fischkoff and Dr Weiss	[A2/1]
October 2001	Abbott Laboratories (Bermuda) Ltd and Abbott Biotechnology Ltd. established in Bermuda	
29 Oct 2001	**Asset Purchase Agreement (non- US rights)** purporting to assign all non-US IP rights relating to D2E7 listed in Schedules 1 and 2 to Abbott Laboratories (Bermuda) Ltd. The sellers were (1) Abbott Deutschland Holding GmbH and (2) Knoll GmbH; the purchaser was Abbott Laboratories (Bermuda) Ltd	[F2.C/35]
29 Oct 2001	**Asset Purchase Agreement (US rights)** purporting to assign all US IP rights relating to D2E7 listed in Schedules 1 and 2 to Abbott Biotechnology Ltd. The sellers were (1) Abbott Deutschland Holding GmbH and (2) Knoll GmbH; the purchaser was Abbott Biotechnology Ltd.	[F2.C/36]

1 Nov 2001	Research and Development Agreement entered into between (1) Abbott GmbH & Co KG, (2) Abbott Laboratories (Bermuda), Ltd. and (3) Abbott Biotechnology Ltd	[F2.B/22/23]
5 June 2002	**US PCT Application** (PCT/US2002/017790) filed by Abbott Laboratories (Bermuda) Ltd (all designated states except US) and Dr Kempeni, Dr Fischkoff and Dr Weiss as the Inventor/Applicants (US only) – US PCT Application (unsigned)	[F2.C/32]
8 June 2002	Priority year ends for US961	
20 Sept 2002	US PCT Application signed by Dr Kempeni, Dr Fischkoff and Dr Weiss – Replacement PCT request with signatures	[F2.C/45]
24 March 2003; 24 August 2003	Dr Fischkoff and Dr Weiss (24 March 2003) and Dr Kempeni (24 August 2003) signed an assignment of all of their rights in US961 to Abbott Biotechnology Ltd. – **USPTO Assignment**	[F2.C/28]
11 July 2003	Dr Fischkoff ended employment with Abbott Laboratories	
July 2003	Abbott Laboratories (Bermuda) Ltd merged into Abbott Biotechnology Ltd. – Amalgamation Agreement	[F2.C/43]
25 June 2012	Abbott Biotechnology Ltd. changed its name to AbbVie Biotechnology Ltd – Change of Name Certificate	[F2.C/44]
9 January 2013	European Patent EP1406656 B1 granted to Abbvie Biotechnology Ltd – EP1406656	[A1/2]
4 November 2014; 11 November 2014	Dr Fischkoff and Dr Weiss (on 4 November 2014) and Dr Kempeni (on 11 November 2014) executed a corrective assignment providing that all ex-US rights in US961 were assigned to Abbott Laboratories (Bermuda) Ltd, effective as of 31 October 2001 – Corrective Patent Assignment.	[F2.C/29]