Federal Court  Cour fédérale

Date: 20210106

Dockets: T-2182-18
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Citation: 2020 FC 1158

Ottawa, Ontario, January 6, 2021

PRESENT: The Honourable Madam Justice Kane

BETWEEN:

TEVA CANADA INNOVATION AND
TEVA CANADA LIMITED

Plaintiffs

and

PHARMASCIENCE INC

Defendant

and

YEDA RESEARCH AND
DEVELOPMENT CO., LTD.

Patentee added pursuant to ss 6(2)
of the *PM (NOC) Regulations* and
ss 55(3) of the *Patent Act*

PUBLIC JUDGMENT AND REASONS

(The Confidential Judgment and Reasons were issued on December 16, 2020 and no redactions are necessary)

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I. Overview

[1] These proceedings involve two patent infringement actions [the Action] pursuant to subsection 6(1) of the *Patented Medicines (Notice of Compliance) Regulations*, SOR/93-133 [the *Regulations*].

[2] At issue are medications that treat multiple sclerosis [MS]. The Teva Canada Innovation and Teva Canada Limited [collectively, Teva] product is Copaxone® [Copaxone]. Copaxone 20

milligram [mg] has been on the market since the mid-90s. Copaxone 40 mg is a more recent product.

[3] The Pharmascience Inc. [Pharmascience] generic product is Glatect® [Glatect]. Pharmascience obtained a Notice of Compliance [NOC] from the Minister of Health [Minister] for Glatect 20 mg, which is administered daily, in 2017 and has been marketing Glatect 20 mg since that time. The Glatect Product Monograph, which, among other things, describes what Glatect 20 mg is intended to treat, is described in more detail later in these Reasons. Teva has confirmed that regardless of the outcome of this Action, the NOC issued to Pharmascience for Glatect 20 mg daily will not be affected.

[4] Pharmascience now seeks to expand its Glatect product to include a 40 mg strength to be administered three times per week. Pharmascience submitted a Supplementary New Drug Submission [SNDS] to do so and, in that context, identified Copaxone 40 mg as the reference product. Pharmascience describes its SNDS as a line extension to its 20 mg product.

[5] This Action arises from Pharmascience's filing of the SNDS. Teva submits that Glatect 40 mg would be marketed in accordance with Pharmascience's proposed Glatect Product Monograph that is substantially identical to Teva's Copaxone Product Monograph.

[6] Teva argues that Pharmascience's Glatect products will infringe the two patents at issue – Canadian Patent Nos. 2,702,437 [the '437 Patent] and 2,760,802 [the '802 Patent]. Teva submits that Pharmascience will manufacture, sell and induce the use of its products, which will be for

exactly the same patient population, in the same dosage strength, and with the same dosage regimen to achieve the same outcomes. Teva submits that Pharmascience has not led any evidence to demonstrate that it will not infringe. Pharmascience argues that the patents are invalid.

[7] The criteria for a diagnosis of MS is a point of contention between Teva and Pharmascience as this has an impact on the scope of the claims of the ‘437 Patent and in turn the allegations of infringement and invalidity. As described below, in the 1980s and 1990s, the diagnosis of MS was based on criteria developed by Poser (Poser CM et al, “New Diagnostic Criteria for Multiple Sclerosis: Guidelines for Research Protocols”, 1983 Ann Neurol 13(3): 227-230 [the Poser criteria]) which required the demonstration of two clinical attacks. In 2001, new criteria were developed by McDonald (McDonald et al, “Recommended diagnostic criteria for multiple sclerosis: guidelines from the international panel on the diagnosis of multiple sclerosis”, 2001 Ann Neurol 50: 121-127 [the McDonald criteria]) which relied more extensively on magnetic resonance imaging [MRI] evidence to demonstrate the disease and its progression. The McDonald criteria were updated in 2005, 2010 and 2017. The experts noted that while the McDonald criteria gained wide acceptance, the Poser criteria and terminology remain within their knowledge and some physicians continue to refer to the Poser criteria.

[8] Teva submits that the claims of the ‘437 Patent are directed only to patients who have had one clinical attack and have not yet been diagnosed with MS.

[9] Teva does not dispute that Copaxone 20 mg was known as an effective therapy for patients diagnosed with relapsing-remitting multiple sclerosis [RRMS], a type of MS. Teva argues that the ‘437 Patent was novel and inventive in identifying 20 mg of glatiramer acetate daily for the early treatment of patients after their first clinical attack and before the onset of MS. Teva argues that the prior art relied on by Pharmascience was obscure and only speculated that glatiramer acetate administered daily would be effective for the early treatment of patients.

[10] Pharmascience argues that it will not infringe the ‘437 Patent because the patent is invalid and because its Glatect 40 mg product is not intended for the single-attack patient but for patients who meet the criteria for a diagnosis of MS or RRMS.

[11] Pharmascience asserts the Gillette defence in response to Teva’s allegations of infringement. Pharmascience argues that it does not infringe the ‘437 Patent because its Glatect product merely practices the teachings of the prior art. Pharmascience submits that the claims of the ‘437 Patent include RRMS patients, and the prior art includes that glatiramer acetate was well known to be an effective treatment for RRMS.

[12] Pharmascience also argues that the ‘437 Patent is neither novel nor inventive and, as a result, is invalid due to anticipation and obviousness.

[13] Pharmascience submits that, although the claims of the ‘437 Patent reflect the Poser criteria, the claims include some patients who meet the McDonald criteria for MS. If Pharmascience’s interpretation prevails, then those patients who have had only one clinical

attack but who meet the criteria for a diagnosis of MS (i.e., based on MRI evidence) would fall within the claims of the ‘437 Patent. Argueably, these MS patients are no different from the RRMS patients for which Copaxone 20 mg was a well-known treatment.

[14] Pharmascience also submits that if the claims of the ‘437 Patent are interpreted narrowly, to single-attack patients (as Teva proposes), the claims are still anticipated by the prior art, which recommended that glatiramer acetate should be considered for the early treatment of such patients.

[15] Pharmascience argues that the claims are obvious because there was no difference between the state of the art in November 2007 and the subject matter of the claims.

[16] Jurisdictional issues have been raised by Pharmascience regarding whether the scope of the *Regulations* permits Teva to assert infringement of the ‘437 Patent with respect to Glatect 20 mg on a go-forward basis in these circumstances, given that Pharmascience has already obtained a NOC. This issue is addressed later in these Reasons in Part XXVI.

[17] With respect to the ‘802 Patent, Teva argues that Pharmascience will infringe the patent because Pharmascience’s Glatect product is indicated for the very same patient population, primarily patients with RRMS, with the same dosing schedule of 40 mg three times weekly. Teva disputes that the ‘802 Patent is invalid for obviousness or lack of sound prediction of utility.

[18] Teva argues that there were material differences between the state of the art in August 2009 and the subject matter of the claims of the patent. Teva disputes that the prior art relied on by Pharmascience was authoritative or known by the person skilled in the art [POSITA or skilled person] or would be considered as a "mosaic" by the POSITA. Teva argues that the POSITA would not reach the invention using their common general knowledge and routine work. Rather inventiveness was required. Teva submits that there is no question that the 40 mg three times per week invention is inventive and useful.

[19] Pharmascience submits that it will not infringe Teva's '802 Patent because the '802 Patent is invalid due to obviousness.

[20] Pharmascience alternatively submits that if the '802 Patent is not obvious based on the prior art, then Teva has neither demonstrated utility nor soundly predicted utility. Teva notes that there are no results set out in the '802 Patent, but only a proposal for a study of the expected results.

[21] Generally, the parties have mapped out different paths to lead to the findings they seek and have pointed to excerpts in the evidence in support of their particular directional paths. However, the role of the Court is to take the "high road" and to consider all the relevant evidence in its proper context.

[22] Both Teva and Pharmascience raised objections to particular evidence of the other party.

[23] For example, Teva submits that Pharmascience has engaged in case splitting by introducing new evidence, in particular, the international patent application WO 2007/081975 [Pinchasi 2007], noted in Dr. Ari Green's responding report on non-infringement. Pharmascience disputes this allegation and argues that it clearly pleaded the Gillette defence as an infringement issue. Pharmascience explains that Dr. Green was given and asked to review the prior art product monographs for Copaxone and Pinchasi 2007 and to describe how a skilled person would understand them. He was also asked to review the Glatect Product Monograph and to provide his opinion as to whether it followed the teachings of the prior art.

[24] Pharmascience explains that it does not rely on Dr. Green's opinion on Pinchasi 2007 in his responding non-infringement report for its anticipation arguments; rather it relies on this evidence for the Gillette defence. Pharmascience notes that Teva did not provide any reply to Dr. Green's non-infringement report.

[25] Pharmascience also notes that it clearly cited Pinchasi 2007 as an anticipatory reference and it can, therefore, be relied on to show anticipation.

[26] Teva also submits that Pharmascience sought to introduce additional evidence in its closing arguments. Pharmascience responds that the additional 21-page compendium contains only excerpts of documents already in evidence to more clearly point to the references Dr. Green relied on in his validity opinion.

[27] More generally, each party seeks to diminish the expertise and evidence of their opponents' experts by, among other things: questioning their understanding of the legal tests and instructions provided; suggesting that they are in the pockets of big pharmaceutical companies due to past research grants and consulting fees; suggesting that they have exceeded their mandates; suggesting that they have not published in certain top scientific journals; suggesting that they have cited other experts in the field in their publications who they now seem to differ with on specific points; and, challenging their specific expertise, such as not being part of a drug development team.

[28] In my view, all the experts have established their particular expertise and all have offered evidence that is helpful to the Court on the issues at play. All the experts are clearly committed to improving the experience of persons with MS. I have considered the submissions of both parties who seek to discount the evidence of the other party's witnesses. I have considered all of the evidence in its proper context and have weighed it. I have not discounted the evidence of any expert because they have been paid by the parties in this or other litigation or in their research, or because they have published more or less extensively than other experts. Clearly, they are all experts in the diagnosis and treatment of MS and have been so qualified for the purpose of this Action. However, the experts have provided different opinions on key issues that are not possible to reconcile. Cross-examination has identified some inconsistencies and frailties in some of the evidence. However, some of the questions posed to the experts on cross-examination were detailed and specific and understandably sought to elicit support for particular arguments. In some instances, the questions and answers were confusing and contrived and have required me to

very carefully consider the totality of the expert's extensive evidence. The assessment of the evidence is addressed in the context of the relevant issues.

[29] For the reasons that follow, I find that the '437 Patent is not anticipated by Karussis D et al, "A recommended treatment algorithm in relapsing multiple sclerosis: report of an international consensus meeting", 2006 Eur J Neurol 13: 61-71 [Karussis 2006]. However, I find that the '437 Patent is obvious.

[30] The jurisdictional issue regarding Teva's reliance on the *Regulations* to allege infringement with respect to the 20 mg Glatect product need not be addressed given my conclusion that the '437 Patent is not valid.

[31] I find that the '802 Patent is valid; it is not obvious and it soundly predicted its utility.

[32] With respect to infringement, if Pharmascience proceeds to market Glatect 40 mg in accordance with its proposed SNDS, it will infringe the '802 Patent.

II. The Patents at Issue

A. *The '437 Patent*

[33] Yeda Research and Development Co., Ltd. [Yeda] is the owner of the '437 Patent.

[34] Pursuant to section 42 of the *Patent Act*, RSC 1985, c P-4 [Patent Act], Yeda has the exclusive right, privilege and liberty of making, constructing, using and selling to others to be used, the invention claimed in the ‘437 Patent.

[35] Yeda is a corporation with a head office in Rehovot, Israel.

[36] Teva Canada Innovation is a corporation with a head office in Montreal Quebec, and an office in Toronto, Ontario. Teva Canada Limited is a corporation with a head office in Toronto, Ontario.

[37] The ‘437 Patent is listed on the Patent Register maintained by the Minister pursuant to the *Regulations* in respect of Teva's 40 mg glatiramer acetate product marketed under the brand name Copaxone in 40 mg/1 mL pre-filled syringes for subcutaneous injection. Teva’s 20 mg strength glatiramer acetate is not listed on the Patent Register.

[38] Teva notes that it has obtained Yeda’s consent for the inclusion of the ‘437 Patent on the Patent Register maintained by the Minister pursuant to the *Regulations*. Teva is authorized by Yeda to sell, and sells, the drug Copaxone (glatiramer acetate) in Canada.

[39] The ‘437 Patent is titled, “Methods of Delaying the Onset of Clinically Definite Multiple Sclerosis”. The ‘437 Patent issued on June 25, 2013 and has not expired.

[40] The parties agree that the relevant date for claims construction is the date of the publication of the patent, June 4, 2009. For anticipation and obviousness, the relevant date is the claim date, November 28, 2007.

[41] The ‘437 Patent contains 50 claims. The claims relate to glatiramer acetate, or medicaments comprising glatiramer acetate, for use in treating human patients at risk of developing MS. The claims at issue (Claims 1, 2, 3, 4, 13, 14, 15, 16, 19, 24, 33, 47 and 50) are set out at Annex 1.

[42] On November 13, 2018, Teva was served with a Notice of Allegation [NOA] from Pharmascience, a generic pharmaceutical company, in respect of Glatect 40 mg regarding the ‘437 Patent. The NOA alleges that the ‘437 Patent would not be infringed by Pharmascience making, constructing, using or selling Glatect and that the ‘437 Patent is invalid.

B. *The ‘802 Patent*

[43] Yeda is also the registered owner of the ‘802 Patent and is a party to this Action pursuant to subsection 6(2) of the *Regulations*.

[44] Pursuant to section 42 of the *Patent Act*, Yeda has the exclusive right, privilege and liberty of making, constructing, using and selling to others to be used, the invention claimed in the ‘802 Patent.

[45] The ‘802 Patent is listed on the Patent Register maintained by the Minister pursuant to the *Regulations* in respect of Teva’s glatiramer acetate product marketed under the brand name Copaxone in 40 mg /1 mL pre-filled syringes for subcutaneous injection.

[46] Teva notes that it has obtained Yeda's consent for the inclusion of the ‘802 Patent on the Patent Register maintained by the Minister pursuant to the *Regulations*. Teva asserts that it is authorized by Yeda to sell, and sells, the drug Copaxone (glatiramer acetate) in Canada.

[47] The ‘802 Patent is titled, “Low Frequency Glatiramer Acetate Therapy”.

[48] The parties agree that the relevant date for construing the claims is the publication date of the patent application, February 24, 2011. The relevant date for the allegations of obviousness is the claim date, August 20, 2009. The relevant date to assess utility is the filing date, August 19, 2010.

[49] The ‘802 Patent contains 66 claims. All claims relate to glatiramer acetate, or medicaments comprising glatiramer acetate, for use in treating human patients with, or at risk of developing, MS. The claims at issue are Claims 1, 2, 3, 4, 22, 24, 25, 36-39, 47-57, 59, 60, 63-66 and are set out at Annex 2.

[50] On November 13, 2018, Teva was served with a NOA from Pharmascience in respect of Glatect regarding the ‘802 Patent. The NOA alleges that the ‘802 Patent would not be infringed by Pharmascience making, constructing, using or selling Glatect and the ‘802 Patent is invalid.

III. The Witnesses and the Nature of their Evidence

[51] The parties presented their evidence in both written reports from fact and expert witnesses and oral testimony from many of the witnesses. The witnesses and a brief synopsis of the nature of their evidence is set out below.

A. *The '437 Patent*

(1) Fact Witnesses for Teva

[52] Ms. Sigalit Zecharia Daniel is the Senior Director, Head of Global Clinical Quality at Teva Pharmaceutical Industries Ltd. Ms. Daniel attached to her affidavit documents related to clinical studies that Teva had conducted, including the clinical study protocols and reports.

[53] Dr. Rivka Kreitman holds a Ph.D. in biochemistry and completed a post-doctoral fellowship in molecular biology and genetics. She joined Teva in 1993 and left in 2018. During her time at Teva, among other things, she and her team were responsible for the research, development, regulatory filings and clinical studies of Copaxone. Dr. Kreitman provided documents related to the development of Copaxone. Dr. Kreitman has also provided evidence in proceedings in other jurisdictions regarding the patents at issue.

(2) Expert Witnesses for Teva

[54] Dr. Sarah Morrow is a neurologist with expertise in neurological disorders, including the diagnosis and treatment of MS. Dr. Morrow described the POSITA, the disclosure of the '437 Patent and the construction of the claims. Dr. Morrow's evidence focussed on whether the using or selling of Pharmascience's Glatect products, as described in the Glatect Product Monograph, would infringe the claims of the '437 Patent.

[55] Dr. Selchen is a neurologist with expertise in neurological disorders, including the diagnosis and treatment of MS. Dr. Selchen responded to Dr. Green's invalidity opinion. Dr. Selchen addressed the POSITA, common general knowledge, construction of the claims and the state of the art in relation to the '437 Patent.

[56] Mr. Neil Palmer is an expert on the Canadian pharmaceutical marketplace. He is the Founder, Senior Adviser, and President Emeritus of PDCI Market Access Inc., an Ottawa-based pricing and reimbursement consultancy. Mr. Palmer's evidence addressed, among other things, the public and private reimbursement regimes relevant to glatiramer acetate including Copaxone and Glatect. The parties agreed that Mr. Palmer's report be accepted without oral testimony.

[57] Dr. Gregory Grant is a biochemist and professor of developmental biology and biochemistry in medicine. Dr. Grant's evidence addressed a biochemist's understanding of "glatiramer acetate" relative to the '437 and '802 Patents and assessed whether Glatect contains

glatiramer acetate. The parties agreed that Dr. Grant's evidence be accepted without oral testimony.

(3) Fact Witnesses for Pharmascience

[58] Mr. Graham McKinnon is a registered patent agent in Canada and the United States. Mr. McKinnon attached to his affidavit documents related to the filing history of the U.S. Patent Application No. 11/651,212 and Canadian Patent No. 2,191,088 [the '088 Patent].

[59] Mr. Deirdre Cozier is the Director of Global Regulatory Affairs at Pharmascience, responsible for compiling information and data and making submissions related to Pharmascience's pharmaceutical products to regulatory authorities worldwide, including Health Canada. Mr. Cozier attached to his affidavit documents related to the regulatory filings of Glatect, including the product monograph and SNDS.

(4) Expert Witnesses for Pharmascience

[60] Dr. Ari Green is a neurologist with expertise in neurological disorders, including the diagnosis and treatment of MS. He provided two reports with respect to the '437 Patent. Dr. Green first set out his opinion on the validity of the '437 Patent and addressed anticipation, citing Karussis 2006, and obviousness with reference to the prior art and common general knowledge. Dr. Green also provided a second report in response to Dr. Morrow's infringement report. In the second report, Dr. Green addressed product monographs, elaborated on the target

patient population and cited additional prior art. Dr. Green has also provided expert evidence in proceedings in other jurisdictions regarding the patents at issue or their equivalents.

[61] Ms. Susanne Picard is a pharmacist and regulatory affairs consultant with expertise in the regulatory approval of pharmaceutical products. Ms. Picard's evidence addressed, among other things, the requirements for New Drug Submissions [NDS] and SNDS, the use of product monographs and, more particularly, the Glatect SNDS and Product Monograph.

B. *The '802 Patent*

(1) Fact Witnesses for Teva

[62] Ms. Sigalit Zecharia Daniel and Dr. Rivka Kreitman, described above, also provided evidence for the '802 Patent.

(2) Fact Witnesses for Pharmascience

[63] Mr. Graham McKinnon and Mr. Deirdre Cozier, described above, also provided evidence for the '802 Patent.

(3) Expert Witnesses for Teva

[64] Dr. Reza Vosoughi is a neurologist with expertise in neurological disorders, including the diagnosis and treatment of multiple sclerosis. Dr.Vosoughi's evidence addressed the POSITA, construction of the claims and infringement of the claims of the 802 Patent.

[65] Dr. Alexandre Prat is a neurologist with expertise in neurological disorders, including the diagnosis and treatment of multiple sclerosis. Dr. Prat responded to Dr. Green's opinion on the invalidity of the '802 Patent.

[66] Dr. Simon Day is a biostatistician with expertise in clinical trial design and interpretation. Among other things, Dr. Day addressed how the POSITA would have regardedthe results of clinincal studies and other abstracts relating to glatiramer acetate.

[67] Mr. Neil Palmer and Dr. Gregory Grant, described above, also provided evidence for the '802 Patent.

(4) Expert Witness for Pharmascience

[68] Dr. Ari Green, described above, also provided his opinion on the validity of the '802 Patent.

IV. MS and its Diagnosis/Criteria

[69] MS is a disease of the central nervous system [CNS], which includes the brain, optic nerve and spinal cord. MS is considered to be an inflammatory or autoimmune disease in which the patient's own immune system attacks the myelin of the CNS.

[70] As explained by Teva's witness Dr. Morrow, and reiterated by the other experts, the CNS is composed of grey matter and white matter. Grey matter contains neuron cell bodies, while white matter contains axons, which are the projecting portions of neurons. The axons of the CNS white matter are wrapped in a fatty substance known as myelin. The myelin forms a sheath (analogous to insulation) that enables rapid transmission of electrical signals generated in neuron cell bodies that are propagated along the length of axons.

[71] With MS, the body's immune system attacks elements of the CNS and leads to the destruction of the myelin sheath in the brain, optic nerve and spinal cord (referred to as "demyelination") and axonal loss, which causes CNS damage, or lesions over time.

[72] Demyelination may occur at various sites within the CNS. The symptoms experienced by an MS patient depend upon the site or sites within the CNS that are affected by demyelination and by the size of the lesions.

[73] Pharmascience's expert, Dr. Green, explained that MS is characterized early on by intermittent but potentially debilitating inflammatory and demyelinating events (also called

"attacks", "relapses", "exacerbations", and "episodes"). One of the common presenting clinical attacks is optic neuritis (which manifests itself as a loss of vision and pain behind the eye). Other common clinical attacks include episodes of numbness, tingling, muscle weakness and spasticity, incoordination, loss of control of bowel and bladder, general fatigue, dizziness and depression.

A. *Types of MS*

[74] The expert witnesses all described the categories of MS in a similar manner noting that the categories are related to the course or progression of the disease.

[75] The experts explained that as of November 2007, with respect to the '437 Patent, and as of August 2009, with respect to the '802 Patent, four distinct clinical courses or categories of MS had been described:

a. RRMS is characterized by intermittent and clearly defined relapses with at least partial recovery or remission of some symptoms over weeks to months;

b. Secondary progressive MS [SPMS], which follows a diagnosis of RRMS is characterized by progressive worsening of symptoms over time with fewer or no intermittent relapses interspersed with periods of partial recovery;

c. Primary progressive MS [PPMS] is characterized by a steady decline in neurological function without distinct relapses or remissions; and,

d. Progressive-relapsing MS [PRMS] is characterized by a steady decline in neurological function from onset overlaid with occasional relapses and periods of recovery during which progressive worsening of symptoms continues.

[76] Several experts explained that RRMS remains the most common type of MS.

B. *Clinically Isolated Syndrome*

[77] Teva's witness, Dr. Selchen explained that, as of November 2007, patients presenting with a single clinical attack having features typical of MS were diagnosed as having a clinically isolated syndrome [CIS]. Dr. Selchen noted that when examining a patient presenting with a possible CIS, it would be important for the clinician to consider whether the CIS is caused by something other than MS. Dr. Selchen also noted that it was recognized that many, but not all, cases of MS begin as a CIS.

[78] MRI could be used for patients who had a single clinical attack to determine if the attack was suggestive or supportive of an MS diagnosis.

[79] Dr. Green also explained that the term CIS was generally applied to patients who had a single episode of clinical neurological worsening that was suspicious for demyelination with MRI evidence of other lesions (at least one or two). CIS with evidence of MRI lesion(s) was often distinguished from an episode that was suspicious for inflammatory demyelination but did

not have MRI lesions by calling it “high risk” CIS. Dr. Green stated that most of these “high risk” CIS patients go on to develop RRMS.

[80] Dr. Green added that the primary means of distinguishing who is at risk of developing future attacks is evidence of prior episodes that preceded the clinical event (the CIS event). As of November 2007, this risk was largely assessed via the identification of suspect lesions on MRI.

C. *Diagnosis of MS*

[81] All the experts agreed that the diagnosis of MS has evolved over time.

[82] The experts also agreed that there is no single diagnostic test for any type of MS. The diagnosis is based on a combination of findings from a patient’s history, physical exam, ancillary diagnostic tests (such as MRIs of the brain and spinal cord) and examination of cerebrospinal fluid through lumbar puncture.

[83] As Dr. Green elaborated, by November 2007, MS diagnosis depended upon (and still depends upon) numerous objective and subjective analyses. Objective analyses include clinical examination, formalized clinical evaluations scored to measure disability, MRI scans, extended clinical assessments (e.g., neuropsychological assessments and neurovisual assessments) and relapse frequency assessments. Subjective assessments include patient questionnaires targeting measurement of clinical progression.

[84] Although MS was diagnosed long before the 1980s, the criteria of relevance to this Action are the Poser and McDonald criteria.

[85] The “Poser criteria” were developed in the 1980s. The Poser criteria depended to a great extent on clinical observation.

[86] The concepts or pillars of the criteria are “dissemination in space” [DIS], described as evidence of lesions at multiple locations in the CNS, and “dissemination in time” [DIT], described as the occurrence of distinct episodes separated in time.

[87] Dr. Green explained that DIT and DIS continue to be crucial characteristic features of MS.

[88] Dr. Selchen also explained that a diagnosis of MS can be made only after demonstration of both DIT and DIS.

[89] Under the Poser criteria, a diagnosis of MS (also referred to as “clinically definite MS” or CDMS) required evidence of multiple CNS lesions. This could be demonstrated by neurological examination (referred to as clinical signs of neurological dysfunction) or by tests and procedures that demonstrate the existence of a lesion without the patient having reported or observed a clinical sign (referred to as paraclinical signs of neurological dysfunction, e.g., relying on MRI). Patients had to have evidence that there was more than one lesion separated in space (i.e., DIS) and evidence of more than one prior episode or relapse (i.e., DIT).

[90] Under the Poser criteria, a diagnosis of CDMS required:

- Two attacks and clinical evidence of two separate lesions; or
- Two attacks and clinical evidence of one lesion and paraclinical evidence (i.e., MRI) of another, separate lesion.

[91] In simpler terms, the diagnosis in accordance with the Poser criteria (and in accordance with the McDonald criteria) requires that the disease is demonstrated to affect different parts of the CNS and at different times.

[92] Dr. Green explained that the Poser criteria initially established that, to make out a diagnosis of CDMS, it was necessary to demonstrate that the disease involved more than one pathway (DIS) and was not "monophasic" (i.e., a single phase) (DIT). This depended on clinical evaluation and typically required that a patient have two identified attacks (i.e., relapses) of more than 24 hours duration separated by more than a one-month interval together with clinical evidence of lesions in at least two different places within the CNS.

[93] Dr. Morrow explained that according to the Poser criteria, a patient that has only experienced one attack and had clinical or paraclinical signs of at least one CNS lesion was referred to as having CIS.

[94] Dr. Morrow stated that the majority of CIS patients progress to being diagnosed with CDMS. Dr. Green agreed. Dr. Selchen also agreed but noted that some patients would need to be followed for a longer period of time.

[95] Dr. Selchen explained that CIS has been called a “clinical event suggestive of MS” because in many patients it precedes a diagnosis of MS.

D. *Use of MRI*

[96] By the early 2000s, MRI was increasingly relied on in the MS clinical setting. Dr. Morrow explained that MRI is a highly sensitive technique for detection of tissue changes in patients with MS. MRI is used as a paraclinical measure for the diagnosis of MS and to monitor both disease activity and progression in patients.

[97] The experts explained how MRI of the brain to identify lesions that are characteristic of MS depicts the disease and its progression and can guide the management of the disease. The two main types of images are “T1-weighted” and “T2-weighted” images.

[98] Dr. Vosoughi and the other experts noted that inflammation in the brain can be observed with the injection of Gadolinium (referred to as Gd or GAD). This was described as an imaging technique in which the patient is given an “enhancing agent”, like a dye, to increase the contrast between healthy and damaged tissues. Dr. Morrow and Dr. Green similarly explained the visualization using MRI T1-weighted images and T2-weighted images and the use of Gd on post-contrast images.

[99] Dr. Vosoughi explained that in patients with MS, T1 lesions tend to increase in number and volume over time. In addition, when the immune system attacks the brain (or spinal cord) in

MS patients, new T2 lesions appear. Over time, the number of T2 lesions and their volume increases. In addition to diagnosis and progression of the disease, the measurement of the number and volume of T1 and T2 lesions is used in clinical trials to monitor the effects of what is being tried.

E. *The McDonald Criteria*

[100] In 2001, the International Panel on MS Diagnosis published a report proposing revised diagnostic criteria for MS, known as the "McDonald criteria". The McDonald criteria permitted the diagnosis of "monosymptomatic" disease (i.e., one attack) suggestive of MS, which was not previously treated as MS, but would have been diagnosed under the Poser criteria as CIS (i.e., patients who had only one confirmed attack). The McDonald criteria also relied on the concepts of DIS and DIT and highlighted the use of MRI along with other diagnostic methods.

[101] Dr. Green noted that the McDonald criteria were developed in response to the need for earlier diagnosis of MS and the increasing use of MRI. Dr. Selchen explained that the McDonald criteria responded to the need to diagnose with specificity and sensitivity; in other words, to identify for treatment those patients that had MS and to exclude from treatment those that did not have MS. MRI provided a means to document DIS and to standardize how to document DIT.

[102] The experts agreed that, by November 2007, it was routine to use MRI findings to confirm a diagnosis of MS.

[103] In accordance with the McDonald criteria, a patient could be diagnosed with MS after a single attack where MRI results could be relied upon to show objective evidence of DIT and DIS (i.e., even if there is no clinical evidence of a second attack or no reporting of a second attack by the patient).

[104] An excerpt from the abstract from McDonald 2001 states:

> The revised criteria facilitate the diagnosis of MS in patients with a variety of presentations, including "monosymptomatic" disease suggestive of MS, disease with a typical relapsing-remitting course, and disease with insidious progression, without clear attacks and remissions. Previously used terms such as "clinically definite" and "probable MS" are no longer recommended. The outcome of a diagnostic evaluation is either MS, "possible MS" (for those at risk for MS, but for whom diagnostic evaluation is equivocal), or "not MS."

[105] The McDonald criteria permitted a diagnosis of MS based on one clinical attack as long as additional evidence was available. Two scenarios were described:

1. One attack with objective evidence of two or more lesions, which required:
    - dissemination in time demonstrated by MRI or
    - a second clinical attack
2. One attack with objective clinical evidence of one lesion (monosymptomatic or CIS), which required:
    - dissemination in space demonstrated by MRI, or
    - two or more MRI detected lesions consistent with MS plus positive cerebral spinal fluid, and

- dissemination in time demonstrated by MRI.

[106] The experts agreed that the McDonald criteria result in a diagnosis of either “MS”, “possible MS” (where the diagnostic evaluation is equivocal) or “not MS”.

[107] All the experts noted how the criteria for diagnosis have evolved and agreed that the McDonald criteria gained general acceptance. The experts agreed that the term CDMS has given way to simply MS. Dr. Morrow explained, however, that the McDonald criteria did not immediately replace the Poser criteria and that practicing neurologists remain familiar with the terms CDMS and CIS. All the experts noted that the POSITA would still be familiar with the terms under the Poser criteria and the McDonald criteria.

[108] The McDonald criteria were refined in 2005, 2010 and 2017.

[109] Dr. Green explained that under the McDonald criteria (Polman et al, “Diagnostic criteria for multiple sclerosis: 2005 Revisions to the “McDonald Criteria”, 2005 Ann Neurol 58: 840-846”), in addition to characteristic symptoms and signs on neurological examination, patients could be diagnosed based on characteristic findings on MRI of the brain and spinal cord. For example, where a patient presented with a history of two episodes or attacks characteristic of MS but only one lesion was confirmed by objective clinical evidence, the McDonald criteria permitted MRI findings to be relied upon to establish that the disease had affected more than one area of the CNS and to support a diagnosis of MS. Alternatively, where neurological examination revealed objective clinical evidence of two or more lesions in the CNS, but the

patient history suggested only one attack, the McDonald criteria permitted MRI findings to be relied upon to establish that the disease was sufficiently disseminated in time to make a diagnosis of MS.

[110] The experts noted that with the introduction of the 2005 McDonald criteria, relatively more CIS patients were diagnosed as having MS (typically RRMS) on the sole basis of appearance of new MRI lesions, regardless of whether new clinical symptoms developed or whether the lesions were "clinically silent".

F. *The Difference between the Poser and McDonald Criteria vis-à-vis a CIS patient*

[111] A point of contention in this Action is whether the claims of the '437 Patent are directed to a single attack (or CIS) patient, i.e., a patient who has had a single attack without more, or are also directed to a single attack patient who meets the McDonald criteria for a diagnosis of MS, but has not yet had a second clinical attack. Teva submits that the claims are clearly directed to administering glatiramer acetate to a CIS patient who has not yet had a second clinical attack and, as a result, has not been diagnosed with CDMS. Teva submits that the claims are not directed at patients who have been or could be diagnosed with MS pursuant to the McDonald criteria.

[112] Pharmascience argues that the McDonald criteria were the applicable diagnostic criteria in 2007 and that some single attack (or CIS) patients that are diagnosed pursuant to the

McDonald criteria with MS and who have not yet had a second attack would also fall within the claims of the ‘437 Patent.

[113] This issue is addressed below in the context of the construction of the claims.

V. Overall Position of the Plaintiff Teva on the ‘437 Patent

[114] Teva notes that its glatiramer acetate product, Copaxone, is a therapy effective for the treatment of patients in the relapsing-remitting phase of MS (i.e., RRMS) to reduce the frequency of clinical relapses.

[115] Teva explains that after the initial approval of Copaxone in the 1990s, it spent over 10 years engaged in research and development to improve its product. Teva notes that it had failures but also successes, notably the invention of the ‘437 and ‘802 Patents.

[116] Teva submits that Pharmascience seeks to benefit from Teva’s hard work, investment and inventiveness.

[117] Teva disputes Pharmascience’s allegation or suggestion that it is seeking to extend the life of its patents, referred to as “evergreening”. Teva acknowledges that its 20 mg Copaxone product has been available for many years. The 40 mg Copaxone product was approved for sale in Canada in 2016. Teva also acknowledges that Pharmascience already obtained a NOC to market its 20 mg glatiramer acetate, Glatect.

[118] Teva explains that it designed and conducted a Phase III clinical trial in the early 2000s (the PreCISe trial) to study the effect of glatiramer acetate in patients who had experienced a single attack suggestive of MS and prior to development of CDMS.

[119] Teva characterizes patients who have experienced a single attack suggestive of MS, but who have not yet been diagnosed with MS, as CIS patients.

[120] Teva filed and obtained the ‘437 Patent based on the results of the PreCISe trial. Teva received regulatory approval for the new indication of CIS in its Product Monograph in 2009.

[121] Teva submits that the claims of the ‘437 Patent are directed to the use of glatiramer acetate to treat CIS patients, including a claim specifying a reduction of at least 50% in new T2 lesions.

[122] Teva submits that Copaxone and Glatect will be used in the same manner if approved in accordance with Pharmascience’s SNDS and draft combined Product Monograph. Teva also submits that Glatect 40 mg would be marketed in accordance with a Product Monograph that is substantially identical to Teva’s Copaxone Product Monograph.

[123] Teva notes that Pharmascience has not provided any evidence to establish non-infringement.

[124] Teva submits that Pharmascience cannot rely on the Gillette defence to infringement. Teva submits that Pharmascience is splitting its case and has taken Teva by surprise by seeking to introduce new evidence in Dr. Green's responding report to the report of Dr. Morrow, Teva's infringement expert. Teva further submits that the law and the facts do not support the Gillette defence.

[125] Teva disputes that the '437 Patent is anticipated by the art cited by Pharmascience, Karussis 2006, discussed more fully below.

[126] Teva also disputes that the '437 Patent is obvious. Teva submits that there are material differences between the state of the art in 2007 – which, among other things, did not establish with any evidence that glatiramer acetate would be effective for CIS patients – and the subject matter of the claims. Teva argues that arriving at the invention required inventiveness.

[127] More generally, Teva alleges that the evidence of Pharmascience's expert on validity, Dr. Green, was inconsistent and should be approached with caution. Teva goes further in challenging Dr. Green's evidence suggesting that Dr. Green went beyond the role of an expert witness and strayed into an advocate for Pharmascience's position.

VI. Overall Position of the Defendant Pharmascience on the '437 Patent

[128] Pharmascience notes that Teva's Copaxone products have benefited from a 20-year monopoly in the Canadian market.

[129] Pharmascience submits that Teva has attempted to extend its monopoly and "evergreen" its invention of glatiramer acetate (Copaxone) through successive patents, which purport to add old uninventive features.

[130] Pharmascience argues that its manufacture, marketing, sale and the overall use of its Glatect products will not infringe the '437 Patent.

[131] Pharmascience raises the Gillette defence against Teva's allegations of infringement of the '437 Patent. Pharmascience submits that it is merely practising the teachings of the prior art which recognized that glatiramer acetate was effective for RRMS and, as a result, Teva's patent is invalid. Alternatively, if Teva's patent is valid it cannot be infringed by Pharmascience.

[132] Pharmascience also argues that the '437 Patent is invalid due to anticipation and obviousness.

[133] Pharmascience submits that, as drafted, the claims of the '437 Patent would encompass patients diagnosed pursuant to the modern and prevailing McDonald criteria. More specifically, patients who have had a single attack but have not yet had a second clinical attack would be included where they meet the criteria for MS pursuant to the McDonald criteria.

[134] Pharmascience notes that, by November 2007, glatiramer acetate was a first-line treatment for patients with RRMS, which would include patients who had experienced a single attack and met the McDonald criteria for MS.

[135] Pharmascience also argues that if the claims are interpreted narrowly, as advanced by Teva, the claims are still anticipated and are obvious.

[136] Pharmascience disputes what it characterizes as Teva's "extreme" position – i.e., that until a Phase III clinical trial had been completed to demonstrate that early treatment of single attack or CIS patients with glatiramer acetate was successful, the use of glatiramer acetate to treat such patients remained novel and inventive.

[137] In support of its position that the '437 Patent is anticipated, Pharmascience points to Karussis 2006. Pharmascience describes Karussis 2006 as the consensus of an international group of 13 MS specialists [the Karussis Working Group] that indicates that glatiramer acetate should be used to treat single-attack patients who meet the McDonald criteria and also those who fall short of meeting the McDonald criteria.

[138] Pharmascience submits that Karussis 2006 indicated that glatiramer acetate "should work" in the treatment of single-attack patients (including those who fell short of the McDonald criteria for MS) and that it would be reasonable to use it to treat such patients.

[139] With respect to anticipation, Pharmascience submits that Karussis 2006 meets the requirements of disclosure and enablement.

[140] Pharmascience further submits that claim 16 of the '437 Patent is anticipated by Pinchasi 2007 as it disclosed the use of 40 mg glatiramer acetate for the treatment of RRMS.

[141] Pharmascience also argues that there are no differences between the state of the art in November 2007, which includes Karussis 2006, and the claims of the ‘437 Patent. As a result, the ‘437 Patent was obvious. Pharmascience submits that, to the extent that there were any differences, these would easily be bridged by the POSITA using the common general knowledge and information found by conducting a reasonably diligent search.

[142] Pharmascience challenges Teva’s reliance on the *Regulations* to obtain declarations of patent infringement in respect of both of Pharmascience’s products – Glatect 20 mg administered daily and Glatect 40 mg administered three times per week – given that Pharmascience obtained a NOC for Glatect 20 mg in 2017 and has been marketing it since that time.

VII. Overall Position of the Plaintiff Teva on the ‘802 Patent

[143] Teva reiterates that it worked over the years to improve its products, including to develop an oral formulation, which proved unsuccessful in a Phase III clinical trial (CORAL), and to develop a 40 mg daily dose of glatiramer acetate, which did not prove to be more effective than the 20 mg dose in the Phase III clinical trial (FORTE).

[144] Teva notes that the ‘802 Patent was the result of a successful Phase III clinical trial (GALA) that showed that 40 mg glatiramer acetate administered three times weekly was effective for the treatment of RRMS.

[145] Teva argues that Pharmascience's Glatect product will infringe the '802 Patent as Pharmascience's product will be used in exactly the same manner as Copaxone 40 mg if it is approved in accordance with Pharmascience's SNDS and proposed draft Product Monograph. Teva notes that Pharmascience has not provided any evidence that it will not infringe, rather it alleges only that the '802 Patent is invalid.

[146] Teva disputes that the '802 Patent is invalid due to obviousness or lack of sound prediction of utility.

[147] Teva submits that Pharmascience has adopted a hindsight approach to obviousness and has "cherry-picked" the prior art, some of which is obscure, to carve a path to show that the state of the art was such that an every other day dose of 40 mg glatiramer acetate was known and that it would be self-evident to simply change the administration to three times a week.

[148] Teva submits that the evidence of its experts should be preferred as it was more balanced. Teva submits that without knowledge of the invention as claimed it would not have been obvious to a POSITA to administer 40 mg glatiramer acetate three times per week to RRMS patients.

[149] Teva notes that Pharmascience has led no evidence to support its argument that the '802 Patent lacks utility. Teva notes that all that is required is a scintilla of utility and there is no doubt that Copaxone 40 mg is useful.

[150] With respect to the allegations regarding lack of sound prediction of utility, Teva notes, among other things, that the ‘802 Patent includes a detailed description of the GALA study, a Phase III clinical trial, including efficacy and safety results of 40 mg glatiramer acetate three times per week, and includes at least 18 references to support the invention.

VIII. Overall Position of the Defendant Pharmascience on the ‘802 Patent

[151] Pharmascience submits that the ‘802 Patent is invalid due to obviousness. Alternatively, it is invalid due to inutility or lack of sound prediction of utility.

[152] Pharmascience submits that Teva had already publicly disclosed an every-other-day dosing regimen for 40 mg glatiramer acetate. Pharmascience relies on a mosaic of the prior art to argue that the state of the art was that 40 mg glatiramer acetate was known to be effective (as was 20 mg) on an alternate day basis. Pharmascience submits that the difference between the state of the art and the claims of the ‘802 Patent is only the difference of one less 40 mg dose in a two-week period. Pharmascience argues that it is easier for a patient to remember to take their medication three times a week on fixed days rather than every other day. Pharmascience argues that the difference between the state of the art and the claims would be easily bridged by the POSITA who would move to the fixed day regime.

[153] Pharmascience also suggests that the Court’s determination of the validity of the ‘802 Patent should be informed by related proceedings. Pharmascience notes that the ‘802 Patent is

being examined by the Canadian Intellectual Property Office [CIPO], and that equivalent patents have been found to be obvious in the U.K. and U.S.

[154] Pharmascience argues that if the ‘802 Patent is not obvious due to the state of the prior art, then Teva cannot resort to the prior art that it discounts or rejects to support the utility or sound prediction of utility of the ‘802 Patent.

[155] Pharmascience argues that the evidence of its experts should be preferred. Pharmascience submits that Teva’s experts were misinstructed regarding the test for obviousness and, more generally, are not of the same caliber as its expert Dr. Green who, among other expertise, is experienced in clinical trial design.

IX. Onus and Burden of Proof

[156] The burden is on the Defendant, Pharmascience, to prove each ground of invalidity on a balance of probabilities. The burden is on the Plaintiff, Teva, to prove infringement on a balance of probabilities. Where the validity of a patent is at issue, the starting point is that the patent is presumed to be valid.

X. The ‘437 Patent – Description and Disclosure

[157] The ‘437 Patent is titled, “Method of Delaying the Onset of Clinically Definite Multiple Sclerosis”.

[158] The ‘437 Patent acknowledges that it cites various publications and that these publications are incorporated by reference into the patent application “to more fully describe the state of the art to which this invention pertains”. These references include: the Poser criteria; Brex PA et al, “A longitudinal study of abnormalities on MRI and disability from multiple sclerosis”, 2002 N Engl J Med 346(3): 158-164 [Brex 2002]; Frohman EM et al, “The utility of MRI in suspected MS: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology”, 2003 Neurology 61(5): 602-611 [Frohman 2003]; Johnson KP et al, “Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind, placebo-controlled trial. The Copolymer 1 Multiple Sclerosis Study Group”, 1995 Neurology 45: 1268-1276 [Johnson 1995]; Cohen JA et al., Rovaris, “9006 Study Group. Randomized, double-blind, dose-comparison study of glatiramer acetate in relapsing–remitting MS”, Neurology, 2007, 68(12): 939-944 [Cohen 2007 or FORTE Phase II]; and, Comi G et al, “European/Canadian Multicenter, Double-Blind, Randomized, Placebo-Controlled Study of the Effects of Glatiramer Acetate on Magnetic Resonance Imaging-Measured Disease Activity and Burden in Patients with Relapsing Multiple Sclerosis”, 2001 Ann Neurol 49: 290-297 [Comi 2001].

[159] In the Background of the Invention, the authors state that MS is “one of the more common chronic neurological diseases in human adults” and that it is a “chronic, inflammatory [CNS] disease characterized pathologically by demyelination” and “classified as an autoimmune disease”.

[160] The ‘437 Patent states that “MS disease activity can be monitored by cranial scans, including [MRI] of the brain, accumulation of disability, as well as rate and severity of relapses”.

[161] The ‘437 Patent further states that that the diagnosis of CDMS as determined by the Poser criteria “requires at least two neurological events suggesting demyelination in the CNS separated in time and in location”.

[162] The ‘437 Patent notes that a CIS is a single monosymptomatic attack suggestive of MS such as optic neuritis, brain stem symptoms, and partial myelitis. It states that “[p]atients with CIS that experience a second clinical attack are generally considered to have [CDMS]” and that “[o]ver 80 percent of patients with a CIS and MRI lesions go on to develop MS, while approximately 20 percent have a self-limited process”.

[163] The ‘437 Patent describes five types of MS: benign, RRMS, secondary progressive MS, progressive relapsing MS and primary progressive MS.

[164] The ‘437 Patent describes glatiramer acetate and notes that it is marketed as Copaxone which had been approved as a 20 mg glatiramer acetate injection for patients with RRMS.

[165] The ‘437 Patent also notes that the synthesis of Copaxone had been disclosed in several U.S. patents and that the formulation of 40 mg Copaxone has been disclosed in a U.S. patent.

[166] The ‘437 Patent further states that the “efficacy of Copaxone® in reducing the frequency of relapses in patients with RRMS is well established” and that both the 20 and 40 mg daily subcutaneous dose have been shown to reduce the total number of enhancing lesions in MS patients as measured by MRI (citing Cohen 2007).

[167] The ‘437 Patent notes that it was an open question whether Copaxone would be effective in patients suffering from earlier stages of MS and that there was a debate in the medical and scientific community as to the benefits of commencing MS therapy at the early stage. It states: “[s]pecifically, questions exist regarding whether the benefits of early treatment outweigh the inconvenience, cost, potential adverse effects of treatment, and the risk of submitting patients that independently of treatment would not experience further events to unnecessary long-term therapy”.

[168] The Summary of the Invention states that the invention “provides a method for delaying the onset of [CDMS] in a patient at risk of developing [CDMS], the method comprising periodically administering a pharmaceutical composition comprising a therapeutically effective amount of glatiramer acetate to the patient, thereby delaying onset of [CDMS] in the patient”.

[169] The Summary adds, among other things, that the invention also provides a method to reduce progression of MRI-monitored disease activity in a patient at risk of developing CDMS, a method for reducing the progression of symptoms, and a method of delaying the progression to CDMS. The Summary adds that the invention of the medicament of glatiramer acetate is for the treatment of a patient who: “experienced a single demyelinating event and an active

inflammatory process, which are indicative of the patient being at high risk of developing CDMS"; and, who "experienced a first clinical event suggestive of [MS] and is at risk of developing [CDMS]".

[170] The '437 Patent sets out definitions of the terms used therein. These definitions are noted in the discussion in Part XV, Construction of the Claims.

[171] The '437 Patent includes five examples to illustrate the invention and to "aid in an understanding of the invention" but not to "limit in any way the invention as set forth in the claims". The examples describe a clinical trial to assess the effect of treatment with daily subcutaneous injections of 20 mg of glatiramer acetate compared to placebo on the time to conversion to CDMS as determined by the Poser criteria. Examples 1, 2 and 5 specifically refer to evaluating the effect of glatiramer acetate on patients presenting with CIS.

[172] The '437 Patent states that the results of the examples "show that early, pre-diagnosis i.e., pre-CDMS, [glatiramer acetate] treatment confers long-term benefits on MS symptoms and on the progression of disability".

[173] The '437 Patent further states that the results show that glatiramer acetate "delays the development of [CDMS] when administered to patients presenting a single, clinically isolated syndrome (CIS) suggestive of MS".

XI. The ‘802 Patent – Description and Disclosure

[174] The 802 Patent is entitled, “Low Frequency Glatiramer Acetate Therapy”.

[175] The ‘802 Patent acknowledges that “[t]hroughout this application various publications are referenced by their full citations. The disclosures of these publications are referenced in this application in order to more fully describe the state of the art”.

[176] In the Background of the Invention, MS is described, as are the various types of MS and methods to monitor the disease. Glatiramer acetate is also described.

[177] The ‘802 Patent explains that patients suffering from RRMS “experience sporadic exacerbations or relapses, as well as periods of remission” and that “[l]esions and evidence of axonal loss may or may not be visible on MRI for patients with RRMS”.

[178] The ‘802 Patent notes that glatiramer acetate “is marketed under the tradename Copaxone®” and that Copaxone as a 20 mg daily injection “is an approved therapy for patients with [RRMS], including patients who have experienced a first clinical episode”.

[179] The ‘802 Patent also notes that “[t]he 20mg/day subcutaneous (s.c.) dose has been shown to reduce the total number of enhancing lesions in MS patients as measured by MRI” and that “[s]afety data accumulated for [glatiramer acetate] in clinical trials shows that the drug product is safe and well tolerated”.

[180] The Summary of the Invention describes a "method of alleviating a symptom of [RRMS] in a human patient suffering from [RRMS] or a patient who has experienced a first clinical episode and is determined to be at high risk of developing [CDMS] comprising administering to the human patient three subcutaneous injections of a therapeutically effective dose of glatiramer acetate over a period of seven days with at least one day between every subcutaneous injection so as to thereby alleviate the symptom of the patient".

[181] The '802 Patent describes several embodiments including "the therapeutically effective dose of glatiramer acetate is 40mg/ml".

[182] Under the Detailed Description of the Invention, the '802 Patent again describes its goal and sets out the several potential embodiments, including several different schedules of three injections per week. Other embodiments describe means of alleviating the symptoms of RRMS, for example, reducing the level of disability and reducing the number of different types of lesions.

[183] The '802 Patent includes the following definitions:

> Immediate post injection reaction (IRPR)" refers to "a reaction such as, palpitations, feeling hot, flushing, hot flushes, tachycardia, dyspnoea, chest discomfort, chest pain, and non-cardiac chest pain that occurs immediately following injection.
>
> Injection site reaction (ISR)" refers to "a reaction such as erythema, hemorrhage, induration, inflammation, mass, pain, pruritus, urticaria, and welt that occurs immediately around the site of injection.
>
> Tolerability" relates to "the level of discomfort associated with [glatiramer acetate] treatment" and "is associated with the frequency and severity of post injection reactions and injection site

> reactions" and "influences the period that a patient can follow [glatiramer acetate] treatment.

[184] Other definitions include, "clinically isolated syndrome", "Gd-enhancing lesions", "single clinical attack", and reference is made to the Poser criteria for a diagnosis of CDMS.

[185] The '802 Patent notes that the example section is set out to aid in understanding of the invention but is not intended to "limit in any way the invention as set forth in the claims".

[186] Experimental Details are set out over 16 pages.

[187] The Discussion notes that a "significant drawback to [glatiramer acetate] therapy is the requirement of daily injections, which can be inconvenient". It adds that "in all clinical trials, injection-site reactions were seen to be the most frequent adverse reactions and were reported by the majority of patients receiving [glatiramer acetate]" (as compared to placebo).

[188] The '802 Patent has 66 claims. The asserted claims are set out in Annex 2. Note that the asserted claims all address the use of 40 mg glatiramer acetate for RRMS patients.

XII. The Structure of this Judgment

[189] As noted, Teva alleges infringement by Pharmascience of both the '437 and the '802 Patents. Pharmascience disputes that it will infringe and alleges that the '437 and '802 Patents are invalid. The principles from the jurisprudence, set out below, apply to the determination of

the issues with respect to both patents. There is some evidence that applies to both patents, including about the treatment of MS. However, other evidence is specific to the patent at issue. The allegations regarding the '437 Patent are addressed first, followed by the allegations regarding the '802 Patent.

XIII. Overview of the Experts' Evidence re the '437 Patent

A. *Pharmascience's Expert, Dr. Green*

[190] Dr. Green described the POSITA as a medical professional (e.g., a neurologist), with experience evaluating and diagnosing patients with MS and administering therapeutic agents for the treatment of MS, who would also be a member of a drug development team.

[191] With respect to the common general knowledge as of November 28, 2007, Dr. Green stated that the POSITA would be knowledgeable about MS and its characteristics, the classification of MS, brain imaging (including the use of MRI), the evolution of diagnostic criteria for MS, CIS, MS therapies (including glatiramer acetate) and CIS therapies (including ongoing clinical studies of glatiramer acetate) and, more generally, the treatment of MS. Dr. Green set out the sources of knowledge, including conferences, journals, online resources such as PubMed and EMBASE (a subscription literature database) and the articles found therein. Dr. Green referred to several reports of studies, suggesting that these were part of the common general knowledge.

[192] Dr. Green stated that generally, the ‘437 Patent relates to the treatment of patients who do not yet have CDMS to delay the onset of CDMS (and the progression of MS-related symptoms). He stated that, more particularly, the ‘437 Patent relates to the use of glatiramer acetate, which was a known treatment for patients suffering CDMS (in particular RRMS), to treat patients who had not yet developed CDMS.

[193] In his written opinion, Dr. Green noted that while all the claims use slightly different language to describe the patient groups, the POSITA would understand that the claimed patient population for all claims is a CIS patient at risk of developing CDMS (and who has not yet developed CDMS) and who presents with at least one lesion consistent with MS.

[194] In his written report in response to Dr. Morrow’s report on validity, and in his oral evidence, Dr. Green opined that the claims also covered patients with MS in accordance with the McDonald criteria.

[195] Dr. Green stated that the inventive concept of the claims of the ‘437 Patent is the same as the subject matter defined by the claims. Other experts agreed.

[196] In Dr. Green’s opinion, the claims of the ‘437 Patent were anticipated. Dr. Green stated that Karussis 2006 both disclosed and enabled the subject matter of all the claims of the ‘437 Patent.

[197] In Dr. Green's opinion, the subject matter of the claims was also obvious. Dr. Green stated that there was no difference between the state of the art in 2007 and the subject matter of the claims disclosed in the '437 Patent.

[198] Dr. Green stated that, by November 2007, a large Phase III clinical study using glatiramer acetate to treat CIS patients was underway (i.e., the PreCISe trial). He also stated that the consensus of leaders in the field was that using glatiramer acetate to treat CIS patients was reasonable and "should work", and that the ongoing clinical study (i.e. the PreCISe trial) was likely to show that early treatment at the time of the initial CIS would have enhanced efficacy compared to later treatment of RRMS.

[199] Dr. Green added that, to the extent that there was any difference between the state of the art and the inventive concept, it would have been easily bridged by the POSITA using the common general knowledge. No inventive ingenuity was required.

[200] Dr. Green explained that the POSITA was aware of the concept of CIS. He added that disease-modifying drugs or therapies [DMDs or DMTs] (e.g., interferons) used to treat MS including RRMS had been shown to be effective in treating CIS patients by reducing the likelihood of progression to CDMS and/or delaying the progression to CDMS. Dr. Green added that the POSITA would be motivated to find new treatments, and glatiramer acetate was the obvious choice.

[201] Dr. Green provided a second written opinion in response to the report on infringement by Teva's expert, Dr. Morrow. Dr. Green's second report addresses several mandates.

[202] Dr. Green indicated that he generally agreed with Dr. Morrow's opinions regarding the scientific and clinical overview of RRMS, description of the POSITA and construction of the claims.

[203] Dr. Green criticised Dr. Morrow's use of the terms "CDMS" and "probable MS" given her acknowledgement that these terms were not used after the McDonald criteria were adopted. In Dr. Green's opinion, the McDonald criteria had replaced the Poser criteria by 2005, at the latest. However, Dr. Green agreed that practicing neurologists remain familiar with the terms CDMS and CIS.

[204] Dr. Green acknowledged that in 2007 a CIS diagnosis would have been for patients who had a single clinical event suggestive of MS.

[205] Dr. Green offered a revised opinion regarding the patients addressed by the claims. In his responding report he stated that "by June 4, 2009, … at least some patients presenting with a single clinical attack and at least one lesion would have been categorized as having MS pursuant to the 2005 McDonald Criteria" and would be included within the claims.

[206] Dr. Green's evidence on this issue is elaborated on in the discussion on the construction of the claims in Part XV.

[207] In his second report, Dr. Green referred to Pinchasi 2007 (a patent application). Dr. Green stated that, as read and understood shortly before November 28, 2007, Pinchasi 2007 directed physicians to use glatiramer acetate to treat patients with RRMS, which would include some patients who had only experienced a single clinical attack. On cross-examination, Dr. Green agreed that a physician would not read Pinchasi 2007 to guide their prescribing practices in 2007 or now.

[208] Dr. Green also provided his opinion on product monographs in general and, more specifically, on the Copaxone 2001 and 2006 product monographs.

[209] Dr. Green stated that, prior to November 2007, he and other physicians prescribed Copaxone to treat CIS patients (i.e., patients who had only experienced a single clinical attack but did not meet the 2005 McDonald criteria to confirm a diagnosis of MS). He acknowledged that this was "off-label" use, meaning uses not approved and not indicated in the product monograph.

[210] Dr. Green was challenged on his inconsistent testimony in proceedings in the U.K. where he suggested that off-label use should only be done in the context of a research study.

B. *Teva's Expert, Dr. Morrow*

[211] Dr. Morrow provided an overview of the scientific and clinical history of MS, including the criteria for its diagnosis, as it relates to the '437 Patent. Dr. Morrow explained that the Poser

criteria for diagnosing MS, which were introduced in the 1980s, used the term CIS for patients who had experienced only a single clinical attack, and CDMS for patients who had experienced at least two clinical attacks.

[212] Dr. Morrow noted that the Poser criteria were gradually replaced by the McDonald criteria, which do not use the terms CIS or CDMS, and do not draw a clear distinction based solely on the number of clinical attacks to make a diagnosis of MS.

[213] Dr. Morrow explained how MRI demonstrates DIT and DIS and that the increasing use of MRI permits the diagnosis of MS without the demonstration of clinical attacks.

[214] Dr. Morrow stated that the POSITA would understand that the language in the claims refers to terms that were used in relation to the Poser criteria (i.e., CDMS), which required the confirmation of a second clinical attack. Dr. Morrow stated that the POSITA would understand that the ‘437 Patent is directed to using glatiramer acetate to treat patients who have had one clinical attack suggestive of MS but have not yet experienced a second clinical attack.

[215] With respect to infringement, Dr. Morrow stated that in her opinion, if Pharmascience’s Glatect product is made, sold, used or constructed in accordance with the Glatect Product Monograph she had reviewed, Glatect 20 mg and 40 mg will be used in the manner set out in the asserted claims of the ‘437 Patent. Dr. Morrow noted the specific wording of the 20 mg product and 40 mg product and the distinctions between them.

C. *Teva's Expert, Dr. Selchen*

[216] Dr. Selchen agreed with Dr. Morrow and with Dr. Green's initial opinion regarding the construction of the claims of the '437 Patent as focussed on the CIS patient.

[217] Dr. Selchen stated that in 2007, a patient presenting with the profile described in claim 1 was typically diagnosed as a patient with CIS. He explained that CIS was treated as distinct from CDMS, which required the confirmation of a second clinical attack (and ruling out other possible non-MS causes for the first attack).

[218] Dr. Selchen emphasized that the claims of the '437 Patent are directed to the CIS patient and not to a patient who could be diagnosed pursuant to the 2001 or 2005 McDonald criteria with MS, including RRMS.

[219] Dr. Selchen noted that the claims of the '437 Patent sets out various modes of efficacy, including: delaying the onset of CDMS; reducing progression of MRI-monitored disease activity (including a reduction in the rate of accumulating new T2-weighted lesions, a measure of active inflammatory process); reducing the progression of symptoms of MS; and, reducing the frequency of relapse.

[220] Dr. Selchen also agreed that the inventive concept of the claims is the subject matter of the claims asserted.

[221] Dr. Selchen did not fully agree with Dr. Green regarding the extent of the common general knowledge, particularly articles from less known journals and those that reported on pilot studies or case reports.

[222] With respect to the allegation of anticipation, Dr. Selchen opined that Karussis 2006 neither disclosed nor enabled a skilled person to practice the subject matter of the claims at issue.

[223] Dr. Selchen noted that the Karussis Working Group was tasked with developing evidence-based recommendations. Karussis 2006 clearly stated that their proposed recommendation for using glatiramer acetate (among other therapies) to treat patients with CIS was not evidence-based. Dr. Selchen stated that the suggestion in Karussis 2006 that the approved therapies "should" work did not single out glatiramer acetate. He stated that the suggestions and opinions would not enable a skilled person to achieve the claimed outcomes of the '437 Patent.

[224] Dr. Selchen acknowledged that in November 2007 the POSITA would have known only that a clinical study had been commenced (i.e., the PreCISe trial). Dr. Selchen also noted that several other clinical trials studying drugs for use in treating MS had failed to meet their objectives and the POSITA would not have assumed the successful outcome of the PreCISe trial simply because the trial had been started.

[225] Dr. Selchen stated that, in 2007, the POSITA would not and could not have treated CIS patients with glatiramer acetate, noting that it was not approved for this use, it would not have

been covered by any drug plan and, more importantly, there was no evidence to support its effectiveness.

[226] Dr. Selchen did not agree with Dr. Green that it would be obvious to the POSITA that glatiramer acetate would be useful to treat CIS as claimed in the ‘437 Patent. Dr. Selchen again noted that there was no evidence that glatiramer acetate had been used to treat patients with CIS, and no evidence of any effect of that treatment, not even from uncontrolled studies or patient case reports.

D. *Teva’s Expert, Dr. Kreitman*

[227] Dr. Kreitman described the PreCISe trial, which demonstrated that 20 mg daily of glatiramer acetate was efficacious in delaying the onset of CDMS in CIS patients. Dr. Kreitman confirmed that the PreCISe trial did not test a 40 mg dose of glatiramer acetate.

[228] Dr. Kreitman also described Teva’ activities leading up to the development of Copaxone 40 mg three times a week and the ‘802 Patent.

[229] Dr. Kreitman noted other trials conducted by Teva, including to test a higher concentration formulation of glatiramer (i.e., 20 mg/0.5 mL), which were abandoned or not successful.

[230] Dr. Kreitman explained that around 2002 Teva began to explore the development of glatiramer acetate 40 mg daily. Teva conducted a Phase III clinical trial, the FORTE trial, which compared 40 mg daily to 20 mg daily of glatiramer acetate. The study failed to show that the 40 mg dose improved efficacy compared to the 20 mg dose.

XIV. The POSITA for the '437 Patent

A. *The Principles from the Jurisprudence*

[231] The jurisprudence refers to this mythical person as the person of skill or the skilled person or as noted above, the POSITA.

[232] The POSITA is not one real person, rather a fictitious person or team of persons with an amalgamation of different skills. The POSITA provides the lens through which the patent is construed, the prior art is considered, and other issues are assessed (*Pfizer Canada Inc v Pharmascience Inc*, 2013 FC 120 at para 28; *Teva Canada Limited v Janssen Inc*, 2018 FC 754 at para 66, aff'd 2019 FCA 273).

[233] In *Valeant Canada LP/Valeant Canada SEC v Generic Partners Canada Inc*, 2019 FC 253 at para 44 [*Valeant*], Justice Fothergill described the POSITA as follows:

> 44. The PSA is unimaginative and uninventive, but reasonably diligent in keeping up with advances (*Pfizer Canada Inc v Teva Canada Ltd*, 2017 FC 777 at para 185). The PSA is not incompetent, and brings background knowledge and experience to the workbench (*AstraZeneca Canada Inc v Apotex Inc*, 2015 FC 322 at para 276). The PSA is not stripped of the ability to pursue

> reasonable and logical enquiries, and can make deductions based on the information available (*Jay-Lor International Inc v Penta Farms Systems Ltd*, 2007 FC 358 at para 75 [*Jay-Lor*], citing *Beloit Canada Ltd v Valmet Oy* (1986), 8 CPR (3d) 289 at 294 (FCA) [*Beloit*]).

B. *Who is the POSITA for the '437 Patent?*

[234] Teva submits that the POSITA is a neurologist with experience in the diagnosis and management of MS.

[235] Pharmascience submits that the POSITA would include a neurologist with several years of experience, including direct experience evaluating and diagnosing patients with MS and administering therapeutic agents for the treatment of MS (including familiarity with their dosing schedules and frequencies of administration). Pharmascience adds that the POSITA would also be part of a drug development team with experience developing clinical studies.

[236] Dr. Green described the POSITA as a medical professional, particularly a neurologist with several years of experience, including direct experience evaluating and diagnosing patients with MS and administering therapeutic agents for the treatment of MS. This would include familiarity with the dosing schedules and frequencies of the different therapeutic agents available for MS treatment, as well as side effects or adverse events that occur with these treatments. Dr. Green added that the POSITA would also be part of a drug development team and have experience with the design of clinical studies. Dr. Green disagreed with Dr. Morrow that the POSITA would also include a biochemist, but agreed that a biochemist could be consulted by the POSITA.

[237] Dr. Selchen agreed that the POSITA would be a medical professional such as a neurologist, with at least a few years' experience evaluating and diagnosing patients with MS and administering therapeutic agents for the treatment of MS. Dr. Selchen did not agree with Dr. Green that the POSITA or team should include a member of a drug development team, or that the POSITA would have experience with the design of studies necessary for drug development. Dr. Selchen opined that this would be too specialized.

[238] The experts all agree on the basic qualifications of the POSITA but disagree on the additional special attributes argued by Pharmascience.

[239] Pharmascience appears to advocate for the POSITA to be part of a drug development team and with experience in the design of clinical studies to later argue that the POSITA would conduct patent searches and would have the skill to conduct clinical studies to the extent that this would be "routine" work.

[240] In my view, the POSITA – through whose eyes the '437 Patent is understood and directed – is a practicing neurologist with several years of experience evaluating, diagnosing and treating patients with MS. This POSITA would be familiar with the therapeutic agents available for the treatment of MS (i.e., the DMTs), their dosing schedules and side effects or adverse events that occur with the various DMTs. The POSITA would have some knowledge of and familiarity with clinical studies and their interpretation but would not be a member of a drug development team. The POSITA is also referred to herein as a practicing neurologist.

XV. The Construction of the Claims

A. *The Principles from the Jurisprudence*

[241] Claims construction is for the court to determine guided by expert evidence if needed. The construction of the claims precedes consideration of the allegations of invalidity. The claims are construed as of the publication date; for the '437 Patent it is June 4, 2009 and for the '802 Patent it is February 24, 2011.

[242] In *Biogen Canada Inc v Taro Pharmaceuticals Inc*, 2020 FC 621 [*Biogen*], the Court summarized the principles of claim construction at paras 76-78, noting at para 78:

> [78] The principles of claim construction were laid out by the Supreme Court of Canada in Whirlpool and Free World Trust (*Whirlpool* at paras 49-55; *Free World Trust v Électro Santé Inc*, 2000 SCC 66 at paras 44-54 [*Free World Trust*]). Claims are to be read in an informed and purposive way, with a mind willing to understand and viewed through the eyes of a POSITA having regard to the common general knowledge. The entire patent specification should be considered in order to ascertain the nature of the invention, however adherence to the claim language allows the claims to be read in the way in which the inventor is presumed to have intended, promoting fairness and predictability.

[243] In *Valeant*, the Court reiterated the "canons of claim construction" at para 42:

> [42] The canons of claims construction are found in the Supreme Court of Canada's decisions in *Whirlpool* at paragraphs 49 to 55 and *Free World Trust v Électro Santé Inc*, 2000 SCC 66 [*Free World Trust*] at paragraphs 44 to 54. They are the following:
>
> > (a) claims are to be read in an informed and purposive way with a mind willing to understand, viewed through the eyes of the person skilled in the

> art as of the date of publication having regard to the common general knowledge;
>
> (b) adherence to the language of the claims allows them to be read in the manner the inventor is presumed to have intended, and in a way that is sympathetic to accomplishing the inventor's purpose, which promotes both fairness and predictability; and
>
> I the whole of the specification should be considered to ascertain the nature of the invention, and the construction of claims must be neither benevolent nor harsh, but should instead be reasonable and fair to both the patentee and the public.

B. *The Claims of the '437 Patent*

[244] The '437 Patent includes definitions of some of the terms used in the patent and in the claims.

[245] The '437 Patent defines a "patient at risk of developing MS (i.e. CDMS)" as a patient presenting any of the known risk factors for MS. The risk factors noted include a CIS, a single attack suggestive of MS without a lesion, the presence of a lesion without a clinical attack, and environmental and genetic factors.

[246] CIS is defined as referring to "a single clinical attack (used interchangeably herein with 'first clinical event' and 'first demyelinating event') suggestive of MS, which, for example, presents as an episode of optic neuritis, blurring of vision, … loss of balance, tremors…[and several other indicators]", and "at least one lesion suggestive of MS".

[247] The ‘437 Patent states that “the criteria as defined by Poser … used to determine if a subject meets the condition consistent with [CDMS] are:

- Two attacks and clinical evidence of two separate lesions or

- Two attacks; clinical evidence of one lesion and paraclinical evidence of another separate lesion.”

[248] An “attack” or “exacerbation, flare, or relapse” are defined clinically as the sudden appearance or worsening of a symptom or neurological dysfunction, with or without objective confirmation.

[249] The ‘437 Patent defines both clinical and paraclinical evidence. Clinical evidence of a lesion is defined as “signs of neurological dysfunction demonstrable by neurological examination” and this includes signs that are no longer present if the sign was recorded by a “competent examiner”. Paraclinical evidence of a lesion that has not produced clinical signs and may or may not have caused symptoms includes evidence from various tests, including neuroimaging.

[250] There are 50 claims in the ‘437 Patent of which 13 are asserted. As noted, the claims are set out in full at Annex 1.

[251] Claim 1 provides:

> A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of

> glatiramer acetate for use in delaying the onset of clinically definite multiple sclerosis in a patient who experienced a single clinical attack suggestive of multiple sclerosis, who presents with at least one lesion consistent with multiple sclerosis and who is at risk of developing clinically definite multiple sclerosis and prior to development of clinically definite multiple sclerosis.

[252] The claim describes the pharmaceutical composition of glatiramer acetate. Subsequent claims make it clear that this is administered as a subcutaneous injection, administered daily in a 20 mg or 40 mg dose.

[253] The claims that address the effects of treatment are not in dispute. These are claims 2 (reducing progression of… (MRI)-monitored disease activity), 3 (reducing the progression of symptoms of [MS]), 4 (reducing the frequency of relapse), 19 and 24 (the relapse rate and the mean number of new T2 lesions) and 33 (the reduction by at least 50% in the rate of accumulating new T2-weighted lesions) and all relate to the patient population described in claim 1.

[254] Claims that describe how glatiramer acetate is administered are also not in dispute: claims 13 (use is once-a-day), 14 (use is subcutaneous), 15 (the therapeutically effective amount of glatiramer acetate is 20 mg) and 16 (the therapeutically effective amount of glatiramer acetate is 40 mg).

[255] Claims 47 and 50 relate to the use of glatiramer acetate in the manufacture of a medicament for the treatment of the patient population set out in claim 1.

[256] The experts all construed the claims in a similar way noting the independent and dependant claims and grouping them according to their similar features. Although all the experts construed claim 1 in the same manner – basically, it means what it says. Teva and Pharmascience interpret the scope of the patient population described in claim 1 differently, which in turn impacts all the claims.

C. *The Dispute regarding the Patients Included in the Claims*

(1) Pharmascience's Submissions

[257] Pharmascience submits that the '437 Patent is clear that its invention, defined in terms of the Poser criteria, is the delay in onset of CDMS in a patient that has suffered a single clinical attack and is at risk of having a second clinical attack (i.e., a CIS patient in accordance with the definition of CIS provided in the '437 Patent).

[258] Pharmascience argues that the claims cover two groups of patients who have experienced a single clinical attack:

- A patient who does not yet meet the MRI criteria to be diagnosed with MS under the 2005 McDonald criteria; and

- A patient who does meet the MRI criteria and is diagnosed or can be diagnosed with MS under the 2005 McDonald criteria.

[259] Pharmascience argues that using the words of the claim and the definitions set out in the ‘437 Patent, the key terms are “single attack” and “prior to the onset of CDMS”, which is specifically defined as a second clinical attack. Pharmascience relies on the McDonald criteria which would result in a diagnosis of MS, based on MRI evidence demonstrating DIS and DIT of lesions, for some patients who experienced only a single clinical attack.

[260] Pharmascience argues that CDMS as defined is not the same as MS or RRMS. Pharmascience submits that a patient could be diagnosed with MS or RRMS pursuant to the McDonald criteria after having only one clinical attack and that this “McDonald MS” patient falls in the claims of the ‘437 Patent because the patient has not yet had a second clinical attack and does not meet the definition of CDMS.

[261] Pharmascience submits that the experts agreed that, due to the use of the “out of date” Poser criteria, the claims cover two groups of single attack patients.

[262] Pharmascience notes that, although its expert, Dr. Green, described the claimed patient population for all claims as being a “CIS patient at risk of developing CDMS (and who has not yet developed CDMS) and presenting with at least one lesion consistent with MS”, Dr. Green repeatedly advised counsel to Teva on cross-examination that he was simply using the definition offered by the patentee, Teva.

[263] Pharmascience also relies on the evidence of Teva’s expert, Dr. Morrow, who described the claims of the ‘437 Patent as relating to “use in patients who meet the diagnostic criteria for

CIS, but do not meet the Poser criteria for CDMS . . . in order to delay the onset of CDMS". Pharmascience suggests that Dr. Morrow's description must be read in light of her opinion on infringement where she stated that the indication for Glatect 40 mg includes within its scope single-attack patients who meet the McDonald criteria.

[264] Pharmascience disputes Teva's proposed narrow construction of the claims. Pharmascience argues that Teva is bound by its choice to use the Poser criteria to draft the claims of the '437 Patent despite that the McDonald criteria were widely accepted and used well before 2007. Pharmascience argues that Teva cannot seek to rewrite the claims with new definitions. Pharmascience adds that if Teva intended to limit the claims it could have drafted the patent clearly to do so.

[265] Pharmascience says that Teva's narrow construction should be rejected as it relies on a construction of the claim language that was rejected by Drs. Green, Selchen and Morrow when they were "properly oriented".

(2) Teva's Submissions

[266] Teva submits that claims 1-4 address the treatment of a patient who experienced a single clinical attack suggestive of MS, presents with at least one lesion consistent with MS, and is at risk of developing CDMS. Teva submits that this is a CIS patient – not a patient who has already been diagnosed or met the criteria of CDMS. Nor is it a patient who has met the criteria of MS pursuant to the application of the McDonald criteria.

[267] Teva submits that all the experts agree that the claims are directed to the treatment of a CIS patient who experienced a single clinical attack suggestive of MS. Teva disputes Pharmascience's interpretation that this includes a CIS patient who meets the McDonald criteria for MS but who has not yet experienced a second clinical attack.

[268] Teva submits that the claims should be construed through the eyes of the POSITA with the common general knowledge as of the claim date, June 4, 2009, which included knowledge of the criteria for diagnosing MS, pursuant to both the Poser criteria and the McDonald criteria.

[269] Teva notes that the McDonald criteria do not require two distinct clinical attacks for a diagnosis of MS. Teva also notes that the experts agreed that reliance on the McDonald criteria led to more CIS patients being diagnosed with MS (typically RRMS) based on the MRI evidence of new lesions regardless of whether new clinical symptoms developed. Teva relies on the evidence of Dr. Morrow who explained that the Poser terms continue to be used and that CIS is understood to be a patient that does not yet meet the diagnostic criteria for MS.

[270] Teva also notes that Dr. Green stated (in his report on validity) that there are several forms of CDMS, including RRMS and that the POSITA would understand that these do not include CIS patients.

[271] Teva also points to Dr. Green's opinion, which was echoed by Dr. Selchen, "[t]hough the claims use slightly different language to describe the patient groups, the skilled person would understand that the claimed patient population for all claims is a CIS patient at risk of developing

CDMS (and who has not yet developed CDMS) and presenting with at least one lesion consistent with MS."

[272] Teva notes that Dr. Selchen clearly explained that "a CIS patient by definition is different than a McDonald patient" and that a single attack patient who meets the McDonald criteria does not fall within the claims.

[273] Teva notes that Dr. Green revised his opinion in response to Dr. Morrow's infringement report but could not explain why he did not state this opinion in his validity report.

[274] Teva submits that Dr. Green's revised opinion is inconsistent with his description of the common general knowledge as reflecting that the patient population was "CIS patients at high risk for developing MS". Teva also notes that the papers cited by Dr. Green, including Comi 2001 and Kappos L et al, "Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes" 2006 Neurology 67: 1242-1249 [Kappos 2006], distinguish CIS patients from patients diagnosed with MS under the McDonald criteria. For example, Dr. Green cited Kappos 2006 which reported on the use of an interferon (i.e., Betaseron® [Betaseron]) in CIS patients (at the time of the initial attack) to prevent future relapses.

D. *What do the Experts Say regarding the Patients Included in the Claims?*

(1) Dr. Green

[275] Dr. Green explained that by 2001, pursuant to the McDonald criteria, there was no longer the requirement for two attacks to confirm the diagnosis and the term CDMS was no longer used – rather the term MS was used. A patient could have one attack yet meet the other McDonald criteria for a diagnosis of MS. If the "one attack" patient did not meet that criteria, they were considered to be a CIS patient.

[276] Dr. Green acknowledged that in 2007 a CIS diagnosis would have been for patients who had a single clinical event suggestive of MS.

[277] He explained that MRI scans of CIS patients did not meet the McDonald criteria, at para 104 of his report:

> MRI scans of such CIS patients, while consistent with MS, did not fulfill the McDonald criteria to enable a confirmed diagnosis of MS. CIS was defined somewhat differently depending on the setting but was generally used to apply to patients who had a single episode of clinical neurological worsening that was suspicious for demyelination (i.e., subacute onset of neurological dysfunction, especially in a young or middle-aged person) with MRI evidence of other lesions (at least 1 or 2 depending on the investigator). Dr. Green acknowledged that in 2007 a CIS diagnosis would have been for patients who had a single clinical event suggestive of MS.

[278] In his validity report, Dr. Green explained that the Summary of the Invention set out in the '437 Patent would be understood by the POSITA as the use of glatiramer acetate to treat CIS

patients and to produce various results, such as delaying the onset of CDMS, delaying progression to CDMS, reducing the progression of MRI-monitored disease activity, reducing the progression of MS symptoms, and reducing the frequency of relapses, among others.

[279] In his second report, which was for the purpose of responding to Dr. Morrow's report on infringement, Dr. Green stated that he generally agreed with Dr. Morrow's interpretation of the claims. Dr. Green then added "by June 2009 (and earlier), which is the date that I was instructed to interpret the claims from the perspective of the skilled person, at least some patients presenting with a single attack and at least one lesion would have been categorized as having MS pursuant to the McDonald criteria".

[280] Dr. Green reiterated this view in his oral testimony, to indicate that the POSITA would understand that the claims include a McDonald MS patient, despite the definition of CIS included in the '437 Patent.

[281] On cross-examination, Dr. Green was directed to para 269 of his validity opinion, where he summarized the claims and stated that the "skilled person would understand that the claimed patient population for all claims is a CIS patient at risk of developing CDMS and presenting with at least one lesion consistent with MS".

[282] Dr. Green acknowledged that he did not explicitly state that his reference to a CIS patient means CIS patients plus "McDonald MS" patients because he had explained this in his opinion on claims construction and he was working from the definitions in the patent. Dr. Green added

that the patent would be read in accordance with the common general knowledge of the time, i.e., the McDonald criteria.

[283] Counsel for Teva questioned why Dr. Green did not state in his validity report that patients who met the McDonald criteria for MS would anticipate or render obvious the patent:

> Are you suggesting to the Court that for the purpose of this validity analysis you say in paragraph 269 it is a CIS patient and you do not say anywhere in the report that McDonald MS patients with one lesion would anticipate or render obvious the patent, treatment of those patients, and it wasn't on purpose?

[284] Dr. Green responded that this was not on purpose. Dr. Green noted that the clinical terminology at the time was imprecise. He stated that he did not change his view, he merely clarified it.

(2) Dr. Morrow

[285] Dr. Morrow explained that the POSITA would understand that the language in claims of the '437 Patent uses terminology in relation to the Poser criteria (e.g., CDMS, an MS diagnosis which requires the confirmation of a second clinical attack). The POSITA would recognize that the '437 Patent is directed to using glatiramer acetate to treat patients who have had one clinical attack suggestive of MS but have not yet experienced a second clinical attack.

[286] With respect to the Poser criteria and CDMS, Dr. Morrow explained that, "to be [CDMS], you needed to have two relapses separated in space, meaning in two different areas of

the CNS. . . . They had to really have two relapses separated by at least 30 days and separated in areas of the brain to show that it was multiple, hence multiple sclerosis."

[287] Dr. Morrow explained that the term CDMS is not used as often today given the development of the McDonald criteria in 2001 and the subsequent iterations. Dr. Morrow explained that when the McDonald criteria are applied, there does not necessarily need to be a second clinical attack because there are other ways to make the diagnosis. She added that the diagnosis would be either CIS or MS (or RRMS) and that the CDMS term has "fallen away".

[288] In Dr. Morrow's oral testimony, she noted that the '437 Patent and the claims use terms derived from the Poser criteria:

> So really we, a person skilled in the art, would understand this means to those who have CIS or one clinical attack suggestive of MS who have not yet met the diagnostic criteria for CDMS or not yet had that second relapse. I guess one more point that is important is under 67.5. Of course that specifically is referring to those who are at risk of developing clinically definite MS. That is where that one other lesion on the MRI becomes important, that you want to see evidence of other inflammation, as well, and of course prior to the development of CDMS, so of course at the CIS stage.

[289] Dr. Morrow explained, as did the other experts, that the McDonald criteria allowed MRI activity to help support a MS diagnosis, in particular by demonstrating DIS and DIT. She explained that the refinements of the criteria have permitted the diagnosis to be made earlier without as much clinical activity. With respect to the different diagnostic criteria, Dr. Morrow explained that pursuant to the McDonald criteria:

> You still need to show multiple areas of the brain and spinal cord involved, as well as multiple over time, but that can now be met

> with MRI criteria. So you can show one relapse and then have areas involved on the MRI that show multiple areas involved in certain areas, and the lesions must look typical for multiple sclerosis. Then dissemination in time or multiple in time to demonstrate that chronicity can be done at the time of the first relapse if they have gad-enhancing lesions, so showing old and new at the same time, or a repeat MRI done after the initial MRI, which shows the development of new lesions, again showing that chronicity, so development of new lesions or multiple over time.

(3) Dr. Selchen

[290] Dr. Selchen did not agree that the claims of the ‘437 Patent included CIS patients who met the McDonald criteria for MS.

[291] Dr. Selchen emphasized that CIS is a separate diagnosis that exists until the second attack or relapse is demonstrated and that there are different implications for the treatment of CIS.

[292] Dr. Selchen stated that, in November 2007, CIS was considered to be distinct from MS. The 2005 McDonald criteria maintained CIS as a separate syndrome. The prevailing view was not simply that “CIS is a form of relapsing MS”, as Dr. Green stated.

[293] Dr. Selchen agreed that scientific publications indicated that many CIS patients and most patients with additional brain lesions would go on to have further attacks. Dr. Selchen also agreed that many patients who would previously have been diagnosed with CIS under the Poser criteria would instead be diagnosed with RRMS according to the McDonald criteria (in 2007 and today).

[294] Dr. Selchen acknowledged that with the advent of MRI evidence and the application of the McDonald criteria, the proportion of patients that develop MS is probably 70-80% but this estimate would depend on how long the patient was followed. Dr. Selchen also agreed with the statement in the ‘437 Patent that by 2003, over 80% of CIS patients with CIS and MRI lesions went on to develop MS. Dr. Selchen added that some CIS patients, for unknown reasons, do not develop MS.

[295] Dr. Selchen noted that a goal of the McDonald criteria was to increase sensitivity without sacrificing specificity in diagnosis. This means that you do not want to miss a patient nor do you want to include a patient in a diagnostic category who does not have the condition.

[296] Dr. Selchen explained that T1 lesions are generally older lesions whereas T2 lesions better represent new inflammatory activity. This made new T2 lesions a useful indicator of active inflammation process (which may or may not be associated with a clinical relapse) and provided a marker that is much more sensitive than clinical relapse as a surrogate for active clinical disease activity.

[297] Dr. Selchen explained that the McDonald criteria allow a patient with a single attack to be characterized as “McDonald positive MS” based on paraclinical, i.e., MRI evidence.

[298] Dr. Selchen stated that the POSITA would understand that CIS patients would not qualify as “confirmed” MS, as this could only be established if and when there was a second attack or the McDonald criteria were met.

[299] On cross-examination, counsel for Teva asked Dr. Selchen whether a patient who presented in November 2007 with a single clinical attack and one or more lesions and met the McDonald criteria for MS, more specifically RRMS, could be treated with glatiramer acetate to delay a second attack and whether this patient would fall within the claims. Dr. Selchen agreed that they could be so treated.

[300] Counsel for Teva described other scenarios, all with respect to the single attack patient who met the McDonald criteria for MS, and asked Dr. Selchen whether this patient could be treated with glatiramer acetate to reduce the progression of MRI-monitored disease activity, to reduce disease progression, to reduce the frequency of relapse, or to address any of the other outcomes set out in the claims. Dr. Selchen agreed that this patient could be so treated.

[301] On re-examination, Dr. Selchen reiterated the opinion set out in his report, which stated that the claims use different language to refer to different patient groups, but that the POSITA would understand that the claims are directed to a CIS patient, not a "McDonald positive" MS patient. Dr. Selchen emphasized that a CIS patient is a patient who does <u>not</u> meet McDonald criteria for MS, who has not yet had a further clinical episode and who has not had MRI lesions showing DIT. Dr. Selchen clearly stated that the CIS and "McDonald positive" MS patients are "totally different patients" by definition. One meets the criteria for a diagnosis of RRMS and the other does not.

E. *The Patients Included in Claim 1 and Subsequent Claims*

[302] The construction of the claims is for the Court to determine. As noted above, the Court construes the claims through the eyes of the POSITA (the practicing neurologist) in a purposive way, with reference to the whole of the specification and to the language used by the inventor, and endeavours to interpret the claims to give effect to the intention of the inventor.

[303] I have considered the disclosure in the ‘437 Patent and the wording of the claims with attention to the definitions in the patent. I have considered the expert evidence that explained the diagnostic criteria for MS and opined on the definitions in the patent. While the common general knowledge as of November 2007 included acceptance of the McDonald criteria to diagnose MS, the experts agreed that the POSITA remained aware of the diagnostic criteria and the terms from both Poser and McDonald. Moreover, the POSITA, being a neurologist with experience treating MS patients, would certainly understand that the intention of the patent and the wording of the claims were directed at early treatment before the onset of MS, regardless of how the diagnosis was reached. The POSITA would be knowledgeable about how MRI (T1 and T2-weighted images as described by the experts) demonstrate DIS and DIT, which are pillars of both the Poser and McDonald diagnostic criteria. The POSITA would understand that CIS is not MS according to the McDonald criteria and is not CDMS according to the Poser criteria. The POSITA would understand that once a patient is diagnosed with, or meets, the criteria to be diagnosed with MS, they are no longer “at risk” of CDMS nor are they “suggestive of MS” as these criteria have been surpassed by the MS diagnosis. The window for the early treatment has passed.

[304] Pharmascience focuses on the terms “single attack” and “before the onset of CDMS”. Pharmascience argues that CDMS means only a second clinical attack and nothing else. Under Pharmascience’s interpretation, a patient who experienced a single attack but has been diagnosed with MS pursuant to McDonald criteria would be included in the claims of the ‘437 Patent. However, this interpretation does not jive with the evidence of the experts who stated that under the McDonald criteria there is no diagnosis of CDMS, just MS or not MS. Two attacks are not needed for a diagnosis of MS pursuant to the McDonald criteria as would be required pursuant to the Poser criteria, which did not rely on MRI evidence to the same extent. Pharmascience accepts and relies on the ‘437 Patent’s use of the Poser criteria but seeks to superimpose the McDonald criteria to expand the coverage of the claims without considering the disclosure in the patent and the lack of logic in this interpretation.

[305] I acknowledge that glatiramer acetate was a known treatment for RRMS well before the ‘437 Patent. I understand that if the claims include MS and RRMS patients, the claims are not novel. I understand that Pharmascience’s interpretation of the claims to include those single attack patients who meet the criteria for MS pursuant to the McDonald criteria would pave the way for a successful Gillette defence and other bases of invalidity. However, this interpretation cannot succeed.

[306] In my view, far too much time and effort was devoted to debating the meaning of the terms, the evolving diagnostic criteria and the scope of the patients covered by the claims.

[307] All the experts construed the claims in accordance with their plain language. The claims mean what they say. Despite this general agreement, Pharmascience's expert, Dr. Green, revised his opinion in his responding report.

[308] I am not persuaded by Dr. Green's revised view that the claims include both CIS patients who do not meet the McDonald criteria and those CIS patients who do meet the McDonald criteria. Dr. Green's evolving evidence seemed to be tailored to support Pharmascience's invalidity arguments and the Gillette defence to infringement. Dr. Green provided confusing responses when offered the opportunity to explain why he revised his opinion. Moreover, his revised opinion discounts the knowledge base of the POSITA.

[309] As noted above, in Dr. Green's report and opinions on validity, he noted the distinction between CIS and CDMS in the patent and explained that the objective of the patent was to determine whether glatiramer acetate would be effective in CIS patients.

[310] Dr. Green explained the importance of demonstrating DIS and DIT, which permit a diagnosis of MS (and also of CDMS). Dr. Green noted the increasing use of MRI to identify the earliest indication of the disease "meaning patients who had a single clinical attack and MRI evidence suggestive of a MS diagnosis (referred to as "Clinically Isolated Syndrome" or "CIS")" and that "MRI scans of such CIS patients, while consistent with MS, did not fulfill the McDonald criteria to enable a confirmed diagnosis of MS."

[311] Dr. Green also stated, with respect to the disclosure of the ‘437 Patent that, “[t]he skilled person would understand that RRMS, SPMS, PPMS and PRMS are all forms of CDMS and that these do not include CIS patients.” [My emphasis]

[312] Dr. Green then modified his view of the claims in his second report in response to Dr. Morrow’s infringement report and stated that the claims included some CIS patients who also met the McDonald criteria for MS, usually RRMS.

[313] Dr. Green attempted to justify his change of opinion by explaining that he had relied on the definitions in the patent in setting out his interpretation of claim 1 in his validity report. Dr. Green’s response on cross-examination to his change of opinion was vague. He could not effectively explain why he did not state in his first report on validity that the claims also included some “McDonald MS” patients.

[314] Dr. Green also inconsistently stated that the concept of CIS was not part of the Poser criteria. However, Dr. Green acknowledged that the ‘437 Patent used the Poser criteria and defined several terms, including the term “clinically isolated syndrome” (and the definition notes that the term is used interchangeably with a “single clinical attack” and “first demyelinating event”). Dr. Green also claimed that he applied these definitions.

[315] On cross-examination, Dr. Green acknowledged that once the patient met the McDonald criteria for MS, they were no longer “suggestive of MS” and they would not meet the criteria of

being “before the onset of CDMS”. Dr. Green stated, “once a patient has McDonald MS, they are no longer a CIS patient”.

[316] Dr. Green also agreed that “single attack suggestive of MS” does not describe a patient that has been diagnosed with MS.

[317] Contrary to Pharmascience’s submission, Dr. Morrow’s evidence does not support their broader interpretation of the claims. Dr. Morrow’s opinion on the construction of the claims, as noted above, is that the claims mean what they say. Her evidence with respect to infringement and the Glatect product is based on the wording of the Glatect Product Monograph, not the claims of the ‘437 Patent.

[318] In her explanation of the claims, Dr. Morrow noted that the POSITA would understand them to be directed to those who have CIS and “of course prior to the development of CDMS, so of course at the CIS stage”.

[319] Dr. Selchen clearly stated that the claims were directed to the CIS patient who did not meet the McDonald criteria for MS. Dr. Selchen noted that a CIS patient is not a MS or a RRMS or a CDMS patient (as also stated by Dr. Green). Dr. Selchen’s responses to various scenarios on cross-examination addressed how the McDonald MS patient could be treated with glatiramer acetate. The treatment of MS or RRMS patient is not in dispute. Dr. Selchen merely confirmed that patients who had been so diagnosed would be treated with glatiramer acetate.

[320] Pharmascience seeks to superimpose the McDonald criteria on the wording of the claims. However, pursuant to the McDonald criteria, a patient would never be diagnosed with CDMS, as that term is not used. Rather, the patient would be diagnosed with MS or "not MS". The experts agree that a patient diagnosed with CDMS has MS. Dr. Green referred to a confirmed diagnosis of MS where the Poser criteria are met. Dr. Green also agreed that RRMS is a form of CDMS and that RRMS and CDMS are not CIS.

[321] All the experts explained that under the Poser criteria the diagnosis was based on clinical observations and assessment. The second clinical attack demonstrated the DIT and DIS of lesions. With the increased reliance on MRI, DIT and DIS could be demonstrated without the observation of a second clinical attack.

[322] The MRI evidence is a surrogate or substitute for the second clinical attack to permit a confirmed diagnosis as both demonstrate DIS and DIT. Under the Poser criteria, the second clinical attack would permit a diagnosis of CDMS. Under the McDonald criteria, the MRI evidence would permit a diagnosis of MS.

[323] The disclosure of the '437 Patent, as described above, acknowledges that 20 mg glatiramer acetate is already approved and effectively used to treat patients with RRMS, which is one of several types of MS. The patent notes that questions existed about the benefits of early treatment. The examples in the patent focus on CIS patients – not those that already meet diagnostic criteria for MS. It is apparent that the intention of the inventors was to focus on early

treatment, i.e., of CIS patient, with the goal of delaying the progress of the disease to CDMS (which is MS).

[324] The plain wording of claim 1 provides that:

- the composition of glatiramer acetate is "for use in delaying the onset of clinically definite multiple sclerosis",

- the target patient population is the patient who:

    - "experienced a single clinical attack suggestive of multiple sclerosis", (CIS is defined as including a single clinical attack and is used interchangeably with first clinical event and first demyelinating event. "[s]uggestive of multiple sclerosis" includes, for example, symptoms of optic neuritis and loss of balance, and means not attributable to another condition.);

    - "presents with at least one lesion consistent with multiple sclerosis";

    - "is at risk of developing clinically definite multiple sclerosis"; and,

    - "presents with [the above] prior to development of clinically definite multiple sclerosis". (In other words, before a second clinical attack.)

[325] When the intention of the Patent and the plain words of the claims are read it would be illogical to interpret the claims to suggest that the single attack is "suggestive of MS" once the

patient already meets the diagnostic criteria of MS. Once a patient is diagnosed with MS, pursuant to the McDonald criteria, they are no longer "suggestive of MS" or of anything other than MS. The patient at that point has MS. On cross-examination, Dr. Green agreed.

[326] Similarly, a patient who "is at risk of developing clinically definite multiple sclerosis" is one that has not yet been diagnosed. Although the patent defines CDMS as two attacks, the experts agreed that CDMS is MS. The POSITA would understand that CDMS is the same as a diagnosis of MS. It would be illogical to characterize patients that have already been diagnosed with MS as "at risk of CDMS". Once diagnosed with MS, the "risk" has materialized.

[327] The claim also focuses on the use of glatiramer acetate in "delaying the onset" of CDMS and "prior to development of [CDMS]". Once CDMS, which is defined as a second clinical attack, is diagnosed, the window for early treatment before its onset has closed. Similarly, once diagnosed with MS, pursuant to the McDonald criteria, the window for early treatment is closed. CDMS is MS and *vice versa*. What else would CDMS be if not MS?

[328] The POSITA in 2007, aware of both the McDonald and Poser diagnostic criteria, reading the claims of the '437 Patent, would know that CDMS is MS and would deduce that the claims are directed to treatment before the onset of the disease and, more particularly, at the CIS stage.

[329] In conclusion, the claims of the '437 Patent are directed to the patient who has had a single clinical attack (or a first demyelinating event) suggestive of MS – a CIS patient – and presents with the criteria set out in the claims before the development of CDMS (which means a

confirmed diagnosis of MS). This does not include patients who have had a single clinical attack but already meet the McDonald criteria for a diagnosis of MS.

XVI. Prior Art related to the '437 Patent

[330] Pharmascience set out 103 prior art references in its Statement of Defence. The experts noted that there were thousands of articles on MS and the treatment for RRMS and CIS. A brief description of the prior art cited and/or referred to is set out below.

[331] A special article published by *Neurology* (Goodin et al, "Disease modifying therapies in multiple sclerosis: Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines" 2002 Neurology 58: 169-178) established guidelines for the treatment of MS. The article noted that "[t]he purpose of this assessment is to consider the clinical utility of these disease-modifying agents including the anti-inflammatory, immunomodulatory, and immunosuppressive treatments that are currently available." The article set out a comprehensive scheme for rating and evaluating data based on the study design, ranking the studies in accordance with the quality of the design and the ability of a study to generate clear and meaningful clinical conclusions. The guidelines noted that evidence based on controlled studies have a higher rating while evidence based on uncontrolled studies, case series, case reports, or expert opinion have a lower rating.

A. *Prior art on the use of glatiramer acetate in MS*

[332] Bornstein et al, "A pilot trial of copolymer 1 in exacerbating-remitting multiple sclerosis" 1987 N Engl J Med 317: 408-414 [Bornstein 1987], was one of the first publications that indicated the efficacy of glatiramer acetate as a treatment capable of reducing relapse rate in patients with MS. Bornstein 1987 was published in the New England Journal of Medicine, acknowledged to be one of the premier journals in the field of medicine.

[333] Johnson 1995 reported on a "pivotal" phase III clinical trial that evaluated the use of glatiramer acetate 20 mg daily subcutaneous to treat RRMS and confirmed the conclusions in Bornstein 1987. In particular, it found that relapses were reduced by approximately 30% in RRMS patients who were treated with 20 mg of glatiramer acetate on a daily basis, compared to placebo.

[334] Comi 2001 reported on a 9-month randomized, double-blind, placebo-controlled trial of RRMS patients given 20 mg daily glatiramer acetate. In addition to the findings in Johnson 1995, Comi 2001 found that RRMS patients treated with glatiramer acetate had a significant reduction in the total number of MRI-measured lesions as compared to placebo.

B. *Prior art on CIS progressing to MS*

[335] Filippi et al, "Quantitative brain MRI lesion load predicts the course of clinically isolated syndromes suggestive of multiple sclerosis" 1994 Neur 44: 635-641 [Filippi 1994] reported on a

5-year study that assessed the likelihood of a CIS patient presenting with brain MRI abnormalities to develop MS within 5 years. It demonstrated that, for patients who had a clinical episode suggestive of a demyelinating attack with brain lesions (i.e. patients with a CIS suggestive of MS), progression to MS occurred in 65% of those patients within 5 years.

[336] Brex 2002 documented a 14-year study following patients with CIS who were clinically suggestive of MS based on MRI analysis. In the introduction, Brex 2002 noted that 90% of patients with MS first present "with isolated syndromes that are clinically suggestive of multiple sclerosis" and that, as of 2002, there were two trials of interferons (CHAMPS and ETOMS) studying the use of "disease-modifying therapies aimed at delaying the onset of multiple sclerosis."

C. *Prior art on the use of interferons in CIS*

[337] Jacobs L.D. et al., Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis (2000) N Engl J Med 343(13): 898-904 [Jacobs 2000] reported on the CHAMPS trial. CHAMPS was a phase III (double-blind, placebo-controlled) clinical trial that studied the use of 30 µg (microgram) subcutaneous interferon beta-1a (i.e. AVONEX® [Avonex]) administered once weekly in CIS patients. The end point was the time until the second clinical attack, which meant that patients who reach the end point would satisfy the Poser criteria for CDMS. Among other things, the results of the trial showed a 58% reduction in the mean number of T2 lesions between the treatment group and placebo.

[338] Comi G et al, “Effect of early interferon treatment on conversion to definite multiple sclerosis: a randomized study”, 2001 Lancet 357: 1576-1582 [Comi 2001 Lancet] reported on the ETOMS trial, which studied the effects of interferon beta-1a (i.e., Rebif® [Rebif]) in CIS patients. ETOMS was a phase III (double-blind, placebo-controlled) clinical trial that studied the subcutaneous use of 22 µg of Rebif administered once weekly in CIS patients. It found that treatment with Rebif reduced the proportion of CIS patients who converted to CDMS as well as reduced the frequency of relapses. Among other things, the results of the trial showed a 33% reduction in the median number of T2 active lesions between the treatment group and placebo. However, this point was disputed between the experts.

[339] Kappos 2006 reported the results of the BENEFIT trial, which was a phase III clinical trial that studied the use of every other day of Betaseron administered by subcutaneous injection in CIS patients. Among other things, the results of the trial showed a 50% risk reduction for progression to CDMS for CIS patients treated with Betaseron compared to placebo. It also showed a 33% reduction in the mean number of T2 lesions.

[340] Comi G and Martino G, “MS treatment: new perspectives”, 2006 Clin Neurol and Neurosurg 108(3): 339-45 [Comi 2006] is a discussion paper that supported early treatment of MS. Among other things, it discussed the CHAMPS and ETOMS trial results. In particular, in comparing patients treated with Avonex in different clinical trials, the authors suggested that the drug seemed to work better, earlier rather than later, in the disease course. Comi 2006 concluded that “[the available] data suggest that early treatment of MS patients with immunomodulatory drugs is advisable.”

[341] Karussis 2006, published in the European Journal of Neurology, is a report of an International Working Group for Treatment Optimization in MS that discussed several statements and refined them, resulting in 15 consensus statements on MS treatment.

[342] Frohman EM et al, "Most Patients with Multiple Sclerosis or a Clinically Isolated Demyelinating Syndrome Should Be Treated at the Time of Diagnosis", 2006 Arch Neurol 63: 614-619 [Frohman 2006] addressed the question of how early MS should be treated. Frohman 2006 noted the results of the ETOMS and CHAMPS trials and set out arguments in favour of early treatment of MS, including for CIS patients.

[343] Pittock SJ et al, "Not every patient with multiple sclerosis should be treated at time of diagnosis" 2006 Arch Neurol 63: 611-614 [Pittock 2006] was cited by Dr. Selchen for the proposition that MRI findings of lesions and long-term disease prognosis in CIS patients remained unclear, reflecting the other side of the debate regarding early treatment.

[344] Panitch H, "Do patients with clinically isolated syndrome benefit from treatment with interferon β1b?" 2007 Nat Clin Prac Neurol 3(2): 81-81 [Panitch 2007] is a one page commentary by Dr. Hillel Panitch on the BENEFIT trial. Dr. Panitch commented that the BENEFIT trial represented the third trial (the others were CHAMPS and ETOMS) to show "essentially the same outcome" in CIS patients. Panitch noted that "a similar large study of glatiramer acetate versus placebo, given the acronym PRECISE, is currently in progress and is likely to show a comparable magnitude of clinical efficacy."

[345] Thrower BW, “Clinically isolated syndromes: predicting and delaying multiple sclerosis.” 2007 Neurology 68(24 Suppl 4): S12-5 [Thrower 2007] reviewed the CHAMPS, CHAMPIONS (an extension of CHAMPS), ETOMS, and BENEFIT clinical trials, all of which investigated the use of DMTs in treating high-risk CIS patients. The author concluded that, “initial trials of immunomodulatory therapies in patients with a CIS indicate that early treatment can delay the second clinical event or new MRI lesion. Therefore, early treatment should be considered for patients who have had a CIS and are at high risk for progression to CDMS.”

[346] Other less well known articles were Tintoré M, “Early MS treatment”, 2007 Int J MS 14: 5-10 [Tintoré 2007], Ruggieri M et al, “Glatiramer acetate in multiple sclerosis: a review”, 2007 CNS Drug Rev 13(2): 178-191 [Ruggieri 2007] and Coyle PK, “Evidence-based medicine and clinical trials”, 2007 Neurology 68 (24 Suppl 4): S3-S7 [Coyle 2007], all of which noted that Teva’s Phase III PreCISe trial was underway.

D. *Prior art cited by Pharmascience as anticipatory references*

[347] Karussis 2006 is cited by Pharmascience as an anticipatory reference. It is described above and below with respect to the allegation of anticipation and obviousness.

[348] Pinchasi 2007 is an international patent application, entitled “Method of treating multiple sclerosis,” filed by Teva on January 9, 2007 and published on July 19, 2007. The patent application describes the invention as “a method of alleviating a symptom of a patient suffering from a relapsing form of multiple sclerosis which comprises periodically administering to the

patient by subcutaneous injection a single dose of a pharmaceutical composition comprising 40 mg of glatiramer acetate so as to thereby alleviate the symptom of the patient. . . . In [one] embodiment, the periodic administration is daily and in another it is every other day."

[349] The Copaxone® 2001 Package Insert and Copaxone® 2006 Product Monograph are cited by Pharmascience. In November 2007, Copaxone was indicated for the treatment of RRMS. At that time, the approved recommended dose for glatiramer acetate was 20 mg daily administered subcutaneously.

XVII. Common General Knowledge

A. *Principles from the Jurisprudence*

[350] As the Court noted in *Valeant* at paras 47-48, the jurisprudence establishes that a patent is construed taking into account the common general knowledge of the POSITA. At para 48, the Court elaborated, citing the principles set out in *Eli Lilly & Co v Apotex Inc*, 2009 FC 991 at para 97 [*Eli Lilly*], aff'd 2010 FCA 240, and *General Tire & Rubber Co v Firestone Tyre & Rubber Co*, [1972] RPC 457 (UKHL) at pp 482-483 [*General Tire*]. The Court noted, among other principles:

- common general knowledge is derived from a common sense approach to the practical question of "what would in fact be known to an appropriately skilled addressee – the sort of person, good at his or her job, who could be found in real life";

- With respect to scientific papers:

    - "it is not sufficient to prove common general knowledge that a particular disclosure is made in an article, or series of articles, or in a scientific journal, no matter how wide the circulation of that journal may be, in the absence of any evidence that the disclosure is accepted generally by those who are engaged in the art to which the disclosure relates"; and,

    - a particular piece of knowledge disclosed in a scientific paper "only becomes general knowledge when it is generally known and accepted without question by the bulk of those who are engaged in the particular art; in other words, when it becomes part of their common stock of knowledge relating to the art".

B. *What Do the Experts Say?*

(1) Dr. Green

[351] Dr. Green noted that as of November 28, 2007, the POSITA would be well versed regarding MS and treatments for MS. The skilled person would have knowledge regarding MS, the characteristics of MS, the classification of MS, brain imaging (including the use of MRI), the evolution of diagnostic criteria for MS, CIS, MS therapies (including glatiramer acetate) and CIS therapies (including ongoing clinical studies of glatiramer acetate). The other experts agreed.

[352] Dr. Green set out the sources of knowledge, including conferences, journals, online resources such as PubMed and EMBASE (a subscription literature database) and the articles found therein.

[353] Dr. Green agreed that, although the POSITA would identify many sources on PubMed and EMBASE, and that he had identified thousands of documents about RRMS and CIS, only some of which included therein would be part of the common general knowledge. Dr. Green acknowledged that he did not refer to EMBASE as a source of common general knowledge in his U.K. reports or in his U.S. reports. Dr. Green ultimately acknowledged that he did not use EMBASE to conduct a search for the purpose of his opinion on the ‘437 Patent.

[354] Dr. Green noted, as did the other experts, that as of November 2007, the available DMTs for MS were interferons (i.e., Avonex, Betaseron, Rebif) and glatiramer acetate (i.e., Copaxone). He also noted Natalizumab and Mitoxantrone.

[355] Dr. Green stated that by November 2007, it was established that glatiramer acetate was effective for RRMS patients in reducing relapses, increasing the time between relapses and reducing MRI activity. In addition, a 40 mg dose had been shown to be equivalently efficacious to the 20 mg dose with some possible advantages in terms of MRI activity.

[356] In Dr. Green’s opinion, by November 2007, it was becoming recognized that treatments for CIS were identical to treatments for MS. Dr. Green cited reports of various studies, including: Comi 2001 Lancet, Kappos 2006, Comi 2006 and Frohman 2006 in support.

[357] Dr. Green stated that Comi 2006 reported that treating early was the prevailing strategy, although some in the field questioned this because of a small subset of patients who may not require treatment.

[358] Dr. Green noted the results of Karussis 2006 and stated that Karussis concluded that because interferons and glatiramer acetate had been shown to be effective in RRMS, and because a CIS patient is highly likely to progress to MS, "it is reasonable to propose early treatment… at the doses approved for MS, even though there is not yet evidence to support this approach."

[359] Dr. Green also referred to Panitch 2007, which reported that the PreCISe trial was in progress and that it was "likely to show a comparable magnitude of clinical efficacy" as the BENEFIT trial, which showed a 50% risk reduction for progression to CDMS for CIS patients treated with interferon beta-1b (i.e., Betaseron).

[360] Although Dr. Green cited Karussis 2006, Panitch 2007, Tintoré 2007, Ruggieri 2007 and Coyle 2007 and suggested that these were part of the common general knowledge, he agreed that these reports were not published in top journals.

[361] With respect to some of the papers cited, including Karussis 2006 and Panitch 2007, Dr. Green acknowledged that he had not set these out as common general knowledge in his U.K. opinion.

[362] Dr. Green acknowledged that he had identified different journals as part of the common general knowledge in his opinion for the U.K. litigation than for the ‘437 Patent. Dr. Green noted there was “overlap” between the common general knowledge in the U.K. and Canada.

[363] Dr. Green also agreed that not everything publicly available on the priority date is part of the common general knowledge.

[364] Dr. Green agreed that Class 1 evidence comprised randomized, double-blind clinical trials and were the “gold standard”. Dr. Green acknowledged that a case report would be a lower classification than Class 3 evidence but stated that a case report still constitutes an important part of the knowledge base.

[365] On cross-examination**,** Dr. Green appeared to acknowledge that Pinchasi 2007 and the ‘088 Patent (both of which were patent applications) did not turn up in the patent search conducted with respect to the ‘437 Patent. Dr. Green noted that he did not personally conduct a patent search related to the ‘437 Patent, but directed the search. Dr. Green stated that the POSITA would know that there were patents on the topics but not the specific information.

[366] With respect to the role of product monographs (also referred to as product labels or inserts) as common general knowledge, Dr. Green stated that physicians do not read or rely on them. Dr. Green explained that the skilled person was aware of approved therapies for reasons other than the product label, but they would know the pertinent facts on the product label.

(2) Dr. Selchen

[367] Dr. Selchen agreed with Dr. Green regarding the common general knowledge about MS and its treatment (as described above) and about many of the sources of that knowledge.

[368] Dr. Selchen agreed that the POSITA would have used online resources, including PubMed, but expressed the view that most neurologists would not have consulted EMBASE or other subscription-based literature searching services.

[369] Dr. Selchen noted that not all the references set out in the ‘437 Patent would have been well known to the POSITA, as some are webpages and others are obscure journal articles or are of limited interest, and that many internationally circulated journals would not have been consulted regularly by neurologists in November 2007 because they were not considered leading journals in the MS field. Dr. Selchen stated that information obtained from patent searches would not be considered common general knowledge, unless the same information was also reported in clinical studies.

[370] Dr. Selchen noted that it was extremely improbable that a clinical neurologist would consult a patent application and that he had never done so. He added that a clinical neurologist would not likely conduct a patent search or to request that this be done to guide clinical decisions. However, he agreed that the skilled neurologist could read and understand patents directed to the field of neurology.

[371] With respect to knowledge of treatment for RRMS**,** Dr. Selchen explained that "first-line therapy" for RRMS in 2007 was typically interferons or glatiramer acetate.

[372] Dr. Selchen agreed with Dr. Green regarding the common general knowledge regarding the effectiveness of treatments for RRMS, for example Comi 2001, which reported that RRMS patients given 20 mg of glatiramer acetate daily had significant reduction in the total number of MRI-measured lesions and relapse rates compared to placebo.

[373] Dr. Selchen also agreed that Cohen 2007, which stated that 40 mg of glatiramer acetate daily was safe and potentially more effective than the 20 mg daily dose, was also known. However, Dr. Selchen pointed out that this was not demonstrated and, as Cohen noted, a "larger, longer study" would be needed.

[374] Dr. Selchen did not agree with Dr. Green that by 2007, it was recognized that CIS treatments were identical to MS treatments.

[375] Dr. Selchen noted that for patients with CIS the tension was between early treatment, given that there was evidence that early treatment may lead to improvements, and delayed treatment, given that not all CIS patients progressed to MS and some did well without any treatment.

[376] Dr. Selchen explained that, in 2007, opinions varied about whom to treat and when to start treatment. One school of thought was that it was best to observe a period of no treatment

and monitor for disease activity for a year to establish whether the diagnosis could be made based on the McDonald criteria (citing Panitch 2007).

[377] Dr. Selchen added that "the desire to begin therapy as soon as possible was not universal", noting that this had to be balanced against not providing treatment (due to its expense, risk of adverse impacts and other considerations) to patients who would unlikely benefit from the treatment, including the many CIS patients who never experience another clinical attack.

[378] Dr. Selchen explained that for those who advocated for early treatment, the standard of care was "trending" toward using interferons for CIS upon diagnosis. He acknowledged the existence of evidence in the treatment of CIS with interferons based on the ETOMS, CHAMPS, and BENEFIT trials. However, he noted that there were neither reports nor evidence of the effects of the use of glatiramer acetate in CIS patients.

[379] Dr. Selchen noted the need for caution when drawing inferences about glatiramer acetate from the efficacy of treatment with interferons on CIS patients because the mechanism of action for these treatments was not clear.

[380] Dr. Selchen also acknowledged that in "Early treatment" 2006 Neurol Sci 27: S8-S12, Professor Comi reported some evidence that glatiramer acetate appeared to be more effective in RRMS patients at earlier stages.

[381] Dr. Selchen took issue with Dr. Green's statement that a number of trials had maintained and even enhanced efficacy for reducing the relapse rate or delaying time to next relapse, reducing evidence of new injury on MRI and reducing disability progression. Dr. Selchen noted that Dr. Green did not identify the trials he relied on. Dr. Selchen also noted that any evidence for reducing the progression of disability (for example with interferons) was short-term and, at best, controversial.

[382] Dr. Selchen agreed that the relevant common general knowledge evolved between November 28, 2007 and June 4, 2009 due to the publication of the results of the PreCISe trial and the revision to the Copaxone product label to include an indication for patients who have experienced a first clinical episode and have MRI features consistent with MS.

C. *The Common General Knowledge regarding the '437 Patent*

[383] Pharmascience cited 103 pieces of art, but acknowledges that not all the prior art is common general knowledge. Pharmascience submits, in the context of its submissions on obviousness, noted below, and supported by the evidence of Dr. Green, that the POSITA was aware of the treatments for MS, the prevailing view that early treatment of RRMS, in particular CIS, was preferable and several studies supported this view, including the statements in Karussis 2006, if not Karussis itself.

[384] Teva agrees that the relevant common general knowledge included the approved treatment therapies for MS (RRMS) available at that time, which were glatiramer acetate (Copaxone) and interferons (Avonex, Rebif, and Betaseron).

[385] Teva notes that there were no test or approvals of glatiramer acetate for CIS, although it was generally known that the PreCISe trial was underway.

[386] Teva submits that early treatment of patients was not part of the common general knowledge. There was no "consensus", rather the debate on whether, when and how to treat continued.

[387] Teva acknowledges that as of November 2007 some interferon therapies were approved for treatment of CIS, but notes that interferons are different compounds than glatiramer acetate.

[388] Teva submits that Karussis 2006 was not common general knowledge, as ultimately acknowledged by Dr. Green.

[389] As noted above in *Valeant* at para 48 common general knowledge is that which would be known to an "appropriately skilled addressed", which means the average, real life POSITA. Not all the articles and reports on studies cited, for example by Dr. Green, were well known or generally accepted and were not part of the "common stock of knowledge".

[390] The Court finds that the common general knowledge as of November 2007 reflected the following:

- knowledge of the characteristics of MS, the classification of MS, brain imaging (including the use of MRI), the evolution of diagnostic criteria for MS, the notion of CIS and MS therapies (interferons and glatiramer acetate);

- for RRMS patients, glatiramer acetate was effective in reducing relapses, increasing the time between relapses and reducing MRI activity, as demonstrated in clinical studies;

- there remained some debate regarding the benefits of early treatment of CIS patients. Although there was a trend toward treating CIS patients with interferons, based on the clinical trials of the interferons that had demonstrated the benefits of early treatment, some experts continued to advocate to wait for a diagnosis of MS;

- interferons were different compounds than glatiramer acetate;

- glatiramer acetate had not been demonstrated to be effective for CIS patients;

- glatiramer acetate was not approved for use for CIS patients;

- it was generally known that the PreCISe trial was underway to determine the effectiveness of glatiramer acetate in CIS patients; and

- Karussis 2006 was not part of the common general knowledge. As noted by Dr. Selchen and acknowledged by Dr. Green, Karussis was not published in a well-known journal. Dr. Green also acknowledged that Karussis was not part of the common general knowledge, although some of the statements in Karussis were. I accept that statements in Karussis 2006 that reflected the diagnostic criteria for MS pursuant to Poser and McDonald and that noted the results of Phase III studies – e.g. of interferons for RRMS and CIS patients and of glatiramer acetate for RRMS patients – would have been common general knowledge. However, the recommendations or suggestions in Karussis 2006 to consider glatiramer acetate for CIS patients were not common general knowledge.

XVIII. Can Pharmascience rely on the Gillette Defence to the Allegations of Infringement of the '437 Patent?

A. *Principles from the Jurisprudence*

[391] The "Gillette defence" is so named due to its origins in *Gillette Safety Razor Co v Anglo-American Trading Co Ltd* (1913), 30 RPR 465 (HL). The defence allows a defendant to deny both the infringement and validity of the patent, and has been referred to as a short cut.

[392] The Gillette defence to a claim of infringement was described in *AB Hassle v Apotex Inc*, 2006 FCA 51 at para 15, as "made out when it is established that the alleged infringing product is based on the teachings of a prior patent."

[393] More recently, in *Tensar Technologies, Limited v Enviro-Pro Geosynthetics Ltd*, 2019 FC 277 at para 135, the Court explained:

> [135] At trial, the Defendant abandoned anticipation as a validity attack, except to the extent that anticipation relates to the Gillette Defence. The Gillette Defence is made out when the alleged infringer can establish that the allegedly infringing product is based on the teachings of a prior art and therefore the alleged infringer is merely doing something that is already known (*Gillette Safety Razor Co v Anglo-American Trading Co Ltd* (1913), 30 RPR 465 (HL)).

B. *Pharmascience's Submissions*

[394] Pharmascience asserts the Gillette defence against the infringement allegations and submits that it is practising the teachings of the prior art and, as a result, the '437 Patent is invalid (as it claims what is in the prior art). Alternatively, if the '437 Patent is valid it cannot be infringed by Pharmascience.

[395] Pharmascience submits that its Glatect product is indicated for the "treatment of ambulatory patients with [RRMS]…to decrease the frequency of clinical exacerbations", which is the same indication that existed for Teva's Copaxone prior to November 2007. Pharmascience notes that 20 mg daily glatiramer acetate was a well-known treatment for RRMS well before 2007.

[396] Pharmascience's reliance on the Gillette defence is based on its view that the target patient population of the claims of the '437 Patent includes both CIS patients that do not meet the McDonald criteria for MS and CIS patients who do meet the McDonald Criteria for MS.

Pharmascience submits that in 2007 glatiramer acetate was already the treatment for McDonald MS patients, who typically have RRMS.

[397] Pharmascience also relies on Pinchasi 2007, which disclosed the use of 40 mg glatiramer acetate for RRMS. Pharmascience submits that this includes the treatment of single-attack patients who are diagnosed with MS under the 2005 McDonald Criteria.

[398] Pharmascience submits that Dr. Green referred to Pinchasi 2007 as a response to Dr. Morrow's infringement report. In addition, Pharmascience cited Pinchasi 2007 as an anticipatory reference.

C. *Teva's Submissions*

[399] Teva argues that the law and the facts do not support Pharmascience's Gillette defence.

[400] Teva submits that to establish the Gillette defence, the alleged infringer (Pharmascience) must show that its activities are actually following the prior art and that the prior art anticipates the claims of the patent.

[401] Teva argues that Pharmascience cannot rely on the Gillette defence to infringement because Pharmascience's proposed Glatect Product Monograph indicates that it is also for the treatment of CIS patients (as does the Copaxone Product Monograph as of 2009). Prior to 2009, Copaxone was not indicated for CIS. Teva points to Dr. Green's evidence on cross-examination

where he acknowledged that the earlier Copaxone labels did not use the same language and did not "call out" its use for CIS and that, at that time, there was no indication for CIS.

[402] Teva further submits that Pharmascience cannot rely on Pinchasi 2007 in support of a Gillette defence. Teva first submits that Pinchasi should be disregarded as it was not referred to in Dr. Green's validity report. Teva also points to Dr. Green's agreement that Pinchasi 2007 did not guide physicians prescribing practices in 2007 or at all and that treating a CIS patient would have been "off label" use in 2007.

D. *The Gillette Defence Cannot Succeed*

[403] Based on the construction of the claims as found above, as targeting patients who have had a single attack or CIS, (i.e., those who have not been diagnosed with CDMS in accordance with the Poser criteria or have not been diagnosed with MS in accordance with the McDonald criteria), the prior art did not teach the use of glatiramer acetate for CIS patients. The prior art taught the use of glatiramer acetate for RRMS patients and this use was well known. The CIS patient is not a MS or RRMS patient.

[404] Pinchasi 2007 was referred to by Dr. Green in response to Dr. Morrow's opinion on infringement and can be considered in the context of the Gillette defence. However, Pinchasi 2007 claims the use of glatiramer acetate 40 mg only for RRMS patients. There is absolutely no mention in Pinchasi 2007 of a single attack patient or CIS. The test results referred to in Pinchasi 2007 are about RRMS patients. Pharmascience's reliance on Pinchasi 2007 and Dr. Green's

evidence that Pinchasi taught the use of 40 mg glatiramer acetate for some single attack or CIS patients is based only on Pharmascience's preferred construction of the claims, which the Court has rejected.

[405] Pharmascience's proposed combined Glatect Product Monograph provides that the 20 mg product is indicated for RRMS patients and patients who have experienced a single demyelinating event (i.e., a CIS patient). Pharmascience's 40 mg product is for RRMS; there is no mention of a CIS patient.

XIX. Is the '437 Patent Anticipated?

A. *Principles from the Jurisprudence*

[406] The test established in *Apotex Inc v Sanofi-Synthelabo Canada Inc*, 2008 SCC 61 [*Sanofi*] governs the determination of anticipation. The Supreme Court of Canada reiterated that anticipation requires disclosure and enablement and elaborated on both requirements. The Court, at paras 25-26, referred to a U.K. decision, *Synthon BV v SmithKline Beecham plc*, [2006] 1 All E.R. 685, [2005] UKHL 59 of Lord Hoffman:

> [25] He explains that the requirement of prior disclosure means that the prior patent must disclose subject matter which, if performed, would necessarily result in infringement of that patent, and states, at para. 22:
>
> > If I may summarize the effect of these two well-known statements [from *General Tire* and *Hills v. Evans*], the matter relied upon as prior art must disclose subject matter which, if performed, would necessarily result in an infringement of the patent. . . . It follows that, whether or not it would be

> apparent to anyone at the time, whenever subject matter described in the prior disclosure is capable of being performed and is such that, if performed, it must result in the patent being infringed, the disclosure condition is satisfied.
>
> When considering the role of the person skilled in the art in respect of disclosure, the skilled person is "taken to be trying to understand what the author of the description [in the prior patent] meant" (para. 32). At this stage, there is no room for trial and error or experimentation by the skilled person. He is simply reading the prior patent for the purposes of understanding it.
>
> [26] If the disclosure requirement is satisfied, the second requirement to prove anticipation is "enablement" which means that the person skilled in the art would have been able to perform the invention (para. 26).

[407] The Supreme Court explained the requirements of enablement at para 27:

> [27] Once the subject matter of the invention is disclosed by the, prior patent, the person skilled in the art is assumed to be willing to make trial and error experiments to get it to work. While trial and error experimentation is permitted at the enablement stage, it is not at the disclosure stage. For purposes of enablement, the question is no longer what the skilled person would think the disclosure of the prior patent meant, but whether he or she would be able to work the invention.

[408] The Supreme Court set out a non-exhaustive list of factors to consider in making the determination of enablement at para 37, including that the POSITA may rely on the common general knowledge to supplement the information in the patent, and that routine trials are acceptable, but prolonged or arduous trial and error would not be considered routine.

[409] In *Tearlab Corporation v I-Med Pharma Inc,* 2019 FCA 179 at paras 73 and 81, the Court of Appeal noted the distinction between anticipation and obviousness, highlighting that

anticipation must be found in a single document, not in a mosaic, as is permitted for the assessment of obviousness, and stated at para 73:

> As noted by Donald MacOdrum in *Fox on the Canadian Law of Patents*, 5th ed., looseleaf (Toronto, Ont.: Thomson Reuters Canada, 2019), at pp. 4-6 and 4-7 [MacOdrum]:
>
> > There is a crucial difference in assessing the effect of prior documents on the question of anticipation and obviousness. When approaching an enquiry as to the novelty of an alleged invention, anticipation must be found in a single document. In other words, it is not legitimate to read several documents together and thus, as the cases put it, to make a mosaic of extracts. In addition, that single document must disclose the precise invention claimed in the patent under attack. But, in considering invention versus obviousness, the prior art should be reviewed and its cumulative effect considered. [References omitted.]

[410] In *Hospira Healthcare Corporation v Kennedy Trust for Rheumatology Research*, 2020 FCA 30 [*Hospira*], the Court of Appeal recently addressed the two requirements for anticipation at paras 66-71, citing the *Sanofi* test.

[411] The Court of Appeal also found that the trial judge erred by conflating the elements of disclosure and enablement and in so doing found that the prior art cited was speculative and, as a result, not anticipatory. The Court of Appeal noted at para 73:

> [73] Though the Judge acknowledged that the test for anticipation has the two distinct requirements of disclosure and enablement as identified in paragraph [66] above, his analysis of the 1994 Kennedy Report and Higgins in the Reasons does not address these requirements distinctly. The Judge appears to have dismissed the appellants' anticipation arguments concerning these two references on the basis that they fail to meet the disclosure requirement because they do not disclose results of the proposed experiments. This approach appears to conflate disclosure and

> enablement. The disclosure requirement is satisfied if performing what is described in the prior art reference would necessarily result in infringement. From a reading of the Reasons, it is not clear how this requirement is not satisfied at least as regards the 1994 Kennedy Report. Even for Higgins, it is not clear how this requirement is not satisfied for those claims that do not include either infliximab or dosing or an administration schedule as an essential element.

B. *Pharmascience's Submissions*

[412] Pharmascience argues that Karussis 2006 anticipates the '437 Patent (except claim 16) regardless of how the claims are construed with respect to the single attack patient. Pharmascience submits that Karussis 2006 satisfies both the disclosure and enablement requirements of anticipation.

[413] Pharmascience notes that the Karussis Working Group reached consensus on several statements and recommended that glatiramer acetate be used to treat single-attack patients who satisfied the McDonald criteria. Pharmascience notes that Karussis 2006 also recommended that glatiramer acetate be used to treat single-attack patients who fell short of satisfying the McDonald criteria. Pharmascience submits that in November 2007, a POSITA could have easily prescribed Copaxone 20 mg daily to treat both groups of patients.

[414] Pharmascience submits that it is beside the point that the 20 mg dosage was not approved or indicated for single attack patients and that its use would be "off label". Pharmascience submits that physicians were not prohibited from prescribing Copaxone. Pharmascience adds that Dr. Green indicated that he and others did so. Pharmascience submits that Teva's experts

acknowledged that off label use occurred. Pharmascience submits that the only issue is whether the POSITA could put the claims into practice based on the teaching of the prior art and clearly they could.

[415] Pharmascience further submits, based on its preferred interpretation that the claims include single attack patients who meet the McDonald criteria for MS, that all claims of the ‘437 Patent, including claim 16 (which claims 40 mg glatiramer acetate), are anticipated by Pinchasi 2007. Pharmascience also argues anticipation by Pinchasi because Pinchasi 2007 also disclosed that a 20 mg dosage had been shown to reduce MRI-measured lesions in MS patients.

[416] Pharmascience notes that, regardless of how the claims are interpreted, the ‘437 Patent states that the “formulation of 40 mg Copaxone® has been disclosed” and in doing so, the POSITA must have been enabled to administer 40 mg glatiramer acetate. Pharmascience submits that Teva is bound by this admission (i.e., regarding claim 16).

[417] Pharmascience disputes Teva’s submission – that because none of the benefits or outcomes of early treatment with glatiramer acetate, as claimed in the ‘437 Patent, were described in the prior art cited – the ‘437 Patent is novel. Pharmascience argues that as long as performing the prior art would result in infringement of the claims, the disclosure requirement of anticipation is met because the benefits or outcomes obtained simply flow from performing the disclosure (*Sanofi* at paras 23-27).

[418] Pharmascience notes that the results of the PreCISe trial demonstrated that 20 mg glatiramer acetate administered to single attack patients will result in all of the claimed benefits (e.g., reducing progression of MRI-monitored disease activity; reducing the progression of symptoms of MS; reducing the frequency of relapse; reducing the mean number of new T2 lesions; and the rate of accumulating new T2-weighted lesions is reduced by at least 50%).

[419] Pharmascience submits that although the POSITA may not have known that these benefits would result, if the POSITA performed the disclosure in Karussis 2006 they would obtain these benefits and they would infringe the claims of the ‘437 Patent.

[420] Pharmascience also disputes Teva’s submission that there is no anticipation when the prior art sets out choices (e.g., the choice between interferons or glatiramer acetate). Pharmascience submits that the issue is whether there is disclosure and enablement of the essential elements of the claims.

[421] Pharmascience disputes Teva’s arguments that Karussis 2006 is not prior art for the purpose of anticipation because it was speculative. Pharmascience submits that anticipation does not require that the prior art be evidence-based; all that is required is that the prior art disclose the invention and enable the POSITA to put it into practice. Pharmascience relies on *Hospira* at para 73 where the Court of Appeal found that it was an error to discount prior art references because they did not disclose the results of proposed experiments.

[422] Pharmascience also points to *Biogen*, where this Court dealt with an anticipatory reference of a study protocol that did not include results. The Court applied *Hospira,* at paras 133-138, and found on the facts of that case that the lack of results from the ongoing study noted in the anticipatory reference was not fatal to the anticipation allegation.

[423] By analogy, Pharmascience submits that the statements in Karussis 2006 and the anticipated results from the PreCISe trial to support those statements are sufficient to meet the disclosure requirement of anticipation.

[424] Pharmascience submits that Teva cannot be rewarded with a patent that took the ideas set out in Karussis 2006. Even if Karussis 2006 did not pursue the recommendations, it disclosed the recommendation.

C. *Teva's Submissions*

[425] Teva reiterates that the patient population addressed in the claims is a CIS patient and does not include a patient who meets the McDonald criteria for MS.

[426] Teva submits that the claims of the '437 Patent are novel and were not anticipated by Karussis 2006 or Pinchasi 2007. Teva submits that Karussis 2006 was a lesser-known article that set out opinions without an evidence base. Teva submits that even if Karussis 2006 is a proper prior art reference, it did not disclose or enable the claims of the '437 Patent as it does not provide a clear direction that would inevitably lead the POSITA to the subject matter claimed in

the patent. Teva submits that Karussis 2006 did not specifically direct the use of glatiramer acetate. Nor did Karussis 2006 provide any disclosure of the benefits or outcomes as claimed in the ‘437 Patent. In addition, the POSITA could not practice the invention in November 2007.

[427] Teva submits that to establish anticipation, a single document must disclose the “precise invention” and provide all information for an enabling disclosure. One document must “disclose exactly and fully what the patentee has claimed” (*Tearlab* at para 81). Teva submits that this is a high threshold to meet and that Karussis 2006 does not satisfy this threshold.

[428] Teva further submits that the benefits of glatiramer acetate to treat CIS patients were not known or contemplated by the prior art cited by Pharmascience (Karussis 2006 or Pinchasi 2007). Teva submits that Karussis 2006 does not disclose the outcomes or benefits set out in the subject matter of the claims. For example, Karussis 2006 does not disclose the therapeutic efficacy of glatiramer acetate to: delay the onset of CDMS; reduce progression of MRI-monitored disease activity; reduce the progression of symptoms of MS; or, reduce the frequency of relapses. Nor does Karussis 2006 disclose a 40 mg dose of glatiramer acetate (claim 16). Teva adds that Karussis 2006 does not disclose any specific therapeutic outcome. Teva notes that claim 33 describes a 50% reduction in new T2 lesions, which was unexpected.

[429] Teva explains that the PreCISe trial was stopped prematurely due to its successful early results that demonstrated “significant and pronounced effects for patients with MRI active disease”. Teva relied on these results to gain approval for this new indication for treating CIS.

Teva relies on *Sanofi*, at para 41, and submits that the beneficial properties demonstrated in the PreCISe trials were not disclosed in the prior art and, as a result, there is no anticipation.

[430] Teva submits that it cannot be said that if a POSITA practices the suggestions in Karussis 2006, it would work to effectively treat CIS patients because there was absolutely no such evidence disclosed in Karussis 2006.

[431] Teva argues that the POSITA would not pursue the recommendations in Karussis 2006. Teva points to the evidence of Dr. Selchen who clearly stated that the "skilled person would have completely rejected this recommendation".

[432] Teva further submits that the reference in Karussis 2006 to clinical trials in progress at that time, cannot anticipate the '437 Patent as Teva's experimental use in the course of the trial does not constitute public disclosure or use.

[433] Teva also argues that Karussis did not enable the POSITA to practice the invention because the use of glatiramer acetate for single attack patients was not approved in 2007.

[434] Teva submits that Dr. Green was inconsistent in his evidence regarding his use of off-label drugs. Teva notes that in this litigation, Dr. Green stated that he prescribes off label and that he and other physicians would have done so in 2007 for glatiramer acetate for CIS patients. However, in the U.K. litigation, Dr. Green stated that he would not change his prescribing

practices even based on a Phase II clinical study; in other words, without evidence of effectiveness.

[435] Teva further submits that Pinchasi 2007 does not anticipate the claims of the ‘437 Patent because Pinchasi 2007 does not disclose the use of glatiramer acetate to treat CIS, rather it discloses its use to treat RRMS. Teva also notes that Dr. Green admitted that a “physician doesn’t read Pinchasi 2007 to guide their prescribing practices”.

D. *What do the Experts Say?*

(1) Dr. Green

[436] In Dr. Green’s opinion, the claims of the ‘437 Patent were disclosed and enabled by Karussis 2006.

[437] Dr. Green noted that Karussis 2006 concluded that “there is evidence that early DMD therapy in patients with a first acute clinical demyelinating event may provide long-term benefit in delaying the progression of the disease and conversion to clinically definite MS”. Dr. Green pointed to the Karussis Working Group’s conclusion that patients that “fall short” of the MS diagnosis pursuant to the McDonald criteria “still warrant consideration for treatment”.

[438] Dr. Green referred to Karussis 2006, which concluded that because interferons and glatiramer acetate had all been shown to be effective in RRMS, and because a CIS patient is

highly likely to progress to MS, “it is reasonable to propose early treatment with these DMDs at the doses approved for MS, even though there is not yet evidence to support this approach”. In his written opinion, Dr. Green stated that Karussis 2006 recommended “not just DMTs generally, but glatiramer acetate specifically for use in CIS patients”.

[439] Dr. Green relied on the statement in Karussis 2006 – that the use of glatiramer acetate in CIS patients (patients with a single attack suggestive of MS and evidence of lesions) “should work” and would be “reasonable” – to support his opinion that Karussis 2006 discloses the subject matter of the claims.

[440] Dr. Green added that Karussis 2006 also enabled the POSITA to implement the invention by specifically indicating that it would be reasonable to treat a CIS patient with glatiramer acetate “at the doses approved for MS”. The POSITA could easily implement this by administering 20 mg glatiramer acetate to CIS patients (the dose approved for MS) and monitoring their progress.

[441] In his oral evidence, Dr. Green stated that prior to November 2007, he and other physicians prescribed Copaxone to treat RRMS patients who had only experienced a single clinical attack. Dr. Green stated that he and other physicians also prescribed Copaxone 20 mg to treat CIS patients (i.e., patients who had only experienced a single clinical attack but did not meet the 2005 McDonald criteria to confirm a diagnosis of MS). Dr. Green acknowledged, however, that he did not state this in his report on validity.

[442] Dr. Green noted that it is common for physicians to prescribe medicines for off-label uses.

(2) Dr. Selchen

[443] Dr. Selchen did not agree with Dr. Green that Karussis 2006 disclosed and enabled (i.e., anticipated) the claims of the ‘437 Patent.

[444] Dr. Selchen described Karussis 2006 as an opinion piece that reflected a consensus among the Karussis Working Group on particular statements that were put to them for discussion. He explained that the focus of Karussis 2006 was on treatment-switching strategies in MS patients already undergoing therapy. Dr. Selchen noted that there was no study or collection of data to underpin the statements or recommendations.

[445] Dr. Selchen acknowledged that the Karussis Working Group agreed that all approved first-line treatments (i.e., interferons and glatiramer acetate) should also work in patients with CIS and may be considered for use in such patients.

[446] Dr. Selchen agreed that in 2007, it was not controversial for the Karussis Working Group to state that patients who fall short of the McDonald criteria “warrant consideration” for treatment. However, the treatment at that time would have been with the tested and approved interferons. Dr. Selchen did not agree that the Karussis Working Group recommended glatiramer

acetate for a CIS patient, rather that this be considered. He added that most POSITAs would have disagreed with this recommendation in 2007 because it was not evidenced based.

[447] Dr. Selchen also noted that Karussis 2006 accepted that some CIS patients may choose not to be treated and prefer to wait for a second attack before beginning treatment.

[448] Dr. Selchen emphasized that although the PreCISe trial was underway to study the use of glatiramer acetate in CIS patients, glatiramer acetate had not been approved to treat CIS patients. Dr. Selchen noted that nothing was known about the efficacy of glatiramer acetate for CIS patients as there had been no previous studies.

[449] Dr. Selchen explained that a practicing clinician would not draw any inferences regarding glatiramer acetate based on their awareness that the PreCISe trial was in progress and would not draw an inference from the results of studies about interferons to recommend or commence off label treatment of glatiramer acetate for CIS patients.

[450] Dr. Selchen added that Karussis 2006 did not disclose the therapeutic benefits or outcomes set out in the claims of the ‘437 Patent. Dr. Selchen disagreed with Dr. Green that a 50% reduction in new T2 lesions was “typical” either of RRMS patients treated with glatiramer acetate or of CIS patients treated with interferons.

[451] With respect to enablement, Dr. Selchen did not agree with Dr. Green that the POSITA would “easily be able to implement” the disclosure of Karussis 2006 to arrive at the subject

matter of the claims. Dr. Selchen explained that the POSITA would not be able to administer glatiramer acetate or determine whether the treatment was therapeutically effective as this would require the conduct of a clinical trial, which is costly, time consuming and requires extensive planning.

[452] Counsel for Pharmascience asked Dr. Selchen whether a physician who followed statement #5 in Karussis 2006 would prescribe 20 mg glatiramer acetate to a CIS patient. Dr. Selchen responded that this was "completely incorrect". He stated that in the "real world" doctors in Canada could not prescribe an unapproved drug: "absolutely, unequivocally no". He added that this would be untenable because there was no evidence to support its effectiveness, as noted by Karussis 2006. Dr. Selchen acknowledged that there was no prohibition on prescribing it off-label, and the drug was available, but that this would not be done in Canada.

E. *Karussis 2006 does Not Anticipate the Claims of the '437 Patent*

[453] As noted, for anticipation, a single piece of prior art must both disclose and enable the subject matter of the claims. Pharmascience relies on Karussis 2006 as the single piece of prior art that anticipates all claims of the '437 Patent except claim 16. Pharmascience relies on Pinchasi 2007, a patent application, as the single piece of prior art that anticipates claim 16.

[454] Pharmascience's submission that claim 16 is disclosed and enabled by Pinchasi 2007 is based on Pharmascience's broader interpretation of the claims, which is rejected. Pinchasi claimed the use of 40 mg glatiramer acetate only for RRMS patients and noted that 20 mg

glatiramer acetate had been disclosed previously for RRMS patients. Pinchasi disclosed test results for RRMS only, not CIS.

[455] I find that Karussis 2006 does not disclose or enable the claims of the ‘437 Patent.

[456] Karussis 2006 and the key statements relied on by Pharmascience must be put in context.

[457] As mentioned above, Karussis 2006 was published in the European Journal of Neurology, noted by Dr. Selchen as not one of the top journals and not well known by the POSITA. Although Karussis 2006 is not common knowledge, some of the references cited are common knowledge. Regardless, it is the prior art relied on.

[458] Karussis 2006 is a report of an International Working Group for Treatment Optimization in MS that discussed several statements and refined them, resulting in 15 consensus statements on MS treatment. The Karussis Working Group did not conduct or propose any experiments or any study protocol. Rather, it considered what had already been studied and noted that other studies were in progress.

[459] As noted by Dr. Selchen, the stated purpose of the Karussis Working Group was to “recommend evidence-based therapeutic options for the management of suboptimal responses or intolerable side-effects in patients treated with disease-modifying drugs (DMDs) for multiple sclerosis (MS).”

[460] Statement #1 provides, "[c]andidates for initiation of DMD therapy should ideally meet the McDonald criteria for the diagnosis of MS". In the discussion regarding this statement, the authors noted the criteria for a diagnosis of MS pursuant to McDonald. They also noted that earlier clinical trials used the Poser criteria for diagnosis.

[461] In the discussion under statement #1, the authors noted "[w]hilst it is accepted that the majority of patients recommended for initiation of DMD therapy should have MS (as described by the McDonald criteria; Table 2), the Working Group agreed that some patients that fall short of fulfilling the McDonald criteria still warrant consideration for treatment". The authors explained that those patients at high risk for developing MS should be considered. They also noted that for those with 'possible MS' special care must be taken before any decisions are made and advice must be sought from an experienced neurologist.

[462] The authors explained that the starting point is that the majority of patients to be treated with DMDs (also referred to as DMTs) should be diagnosed with MS. A subset of patients, at high risk, "warrant consideration for treatment". This wording, noted by Dr. Selchen to be conditional, conveys that it would be somewhat exceptional to treat a patient who falls short of the MS diagnosis with a DMD.

[463] Karussis 2006 statement #4 provides that "[r]ecommendations related to the treatment paradigm should be based on approved agents with proven efficacy in large, Phase III trials in MS; experimental or 'off-label' treatments or combinations cannot be recommended as first line therapies". The authors then noted that three interferons and glatiramer acetate had been shown

to reduce disease activity in Phase III clinical trials in patients with RRMS and CDMS (according to the Poser criteria). The references cited in Karussis 2006 include reports on several Phase III clinical trials. This statement conveys that the authors agree that Phase III clinical trials guide the use of DMDs.

[464] Statement #5, which is relied on by Pharmascience in support of its allegations of invalidity based on anticipation and obviousness, provides that "[a]ll approved first-line DMD treatments can be considered for use after the first demyelinating event in patients at high risk of conversion to MS."

[465] Karussis 2006 includes the following additional observations regarding Statement #5:

- "Whilst [the Karussis Working Group] agreed that all approved first-line treatments ([interferons] and glatiramer acetate…) should also work in patients with CIS and thus may be considered for use in such patients, they accepted that this recommendation is not evidence-based."

- "There are no data with [Betaseron] or glatiramer acetate in patients with a CIS suggestive of MS, although studies are ongoing." The Working Group cited the CHAMPS study, but did not specifically refer to the PreCISe study.

- "They [the Working Group] concluded that, as [interferons] and glatiramer acetate have all been shown to be effective in RRMS, and a patient with a CIS is highly likely to

progress to MS, it is reasonable to propose early treatment with these DMDs at the doses approved for MS, even though there is not yet evidence to support this approach."

[466] In the discussion, which follows the 15 statements, the authors note that "[a] patient with CIS suggestive of MS may prefer to wait for a second attack before beginning treatment. Others may reject treatment with IFN beta or glatiramer acetate because they do not wish to have injections."

[467] In my view, the POSITA would read Karussis 2006 in its entirety with the benefit of their knowledge of MS and would draw distinctions between the statements that are based on evidence and those that are not. The POSITA would understand Karussis 2006 statement #5 to be a carefully worded opinion ("can be considered for use") coupled with the *caveat* about the lack of evidence about the early treatment of CIS patients and that the recommendations of the Karussis Working Group are not prescriptive.

[468] Pharmascience's position – that Karussis 2006 disclosed and enabled the claims of the '437 Patent because Karussis 2006 recommended that glatiramer acetate be used to treat single attack (CIS) patients who fell short of the McDonald criteria for MS – is an over statement.

[469] Dr. Green's evidence in support of this view also overstates some of the Karussis 2006 statements and recommendations and does not reflect the purpose of Karussis 2006 or the full context in which the statements were made. Contrary to Dr. Green's written opinion that "Karussis recommended not just DMTs generally, but glatiramer acetate in particular for CIS

patients", this is not what Karussis 2006 states. Dr. Green conceded on cross-examination that Karussis 2006 does not specifically recommend glatiramer acetate, rather glatiramer acetate is included as one of the approved therapies for MS and Karussis 2006 only suggested that such therapies be considered.

[470] On cross examination, Dr. Green also acknowledged that there were no reports of the effective use of glatiramer acetate in patients with CIS before November 2007; the studies done to that date on glatiramer acetate were with respect to RRMS patients; the studies done to date with respect to CIS patients were of interferons; the Karussis 2006 recommendation referred to all therapies, not glatiramer acetate in particular; Karussis 2006 did not refer to 40 mg of glatiramer acetate; and, Pinchasi 2007 claimed a 40 mg dose of glatiramer acetate for RRMS.

[471] As Dr. Selchen explained, there was no evidence anywhere at that time to support the effectiveness of glatiramer acetate for CIS patients – no Phase II studies, pilot studies or even case reports.

[472] Dr. Selchen noted that in 2007, the determination whether a given MS therapy is effective was (and still is) based on scientific evidence from clinical studies. He explained that there are "classes" of clinical studies, which guide the evaluation of the data presented (as noted in *Neurology*). Class 1 would be a prospective study, randomized, controlled and blinded in a representative population (such as the PreCISe trial). Other experts referred to this type of study as the "gold standard". Dr. Selchen noted that an expert opinion is not a study.

[473] I prefer the evidence of Dr. Selchen who characterized Karussis 2006 as disclosing only the agreement of the thirteen members of the Karussis Working Group that DMTs, including glatiramer acetate, "should" work, "may be considered" for use and that "it is reasonable to propose early treatment". Dr. Selchen regarded the statements in Karussis 2006 as proposals based on a hypothesis and speculation, and not evidence-based as the report acknowledged.

[474] As mentioned above, Dr. Selchen agreed that it was not controversial for the Karussis Working Group to state that patients who fall short of the McDonald criteria "warrant consideration" for treatment, but in his view, the treatment considered at that time would have been with the interferons that had been tested and were approved.

[475] I accept Dr. Selchen's view that the POSITA would not have viewed Karussis 2006 as disclosing glatiramer acetate 20 mg for CIS patients due to the wording of the report, its context and purpose and the lack of any evidence about the efficacy of glatiramer acetate. Karussis 2006 did not disclose fully and exactly what the patent claims and would not lead the POSITA directly to the claimed subject matter of the '437 Patent.

[476] With respect to Pharmascience's submission that anticipation has never required the prior art to be evidence based, the jurisprudence relied on by Pharmascience reflects factual findings that the prior art at issue in those cases met the disclosure requirement (e.g., *Eli Lilly Canada Inc v Mylan Pharmaceuticals ULC*, 2020 FC 816; *Hoffman-La Roche Limited v Apotex Inc*, 2013 FC 718; and *Shire Biochem Inc v Canada (Health)*, 2008 FC 538). The jurisprudence relied on does not set out any general proposition.

[477] As noted above, Pharmascience submits that as in *Hospira* and *Biogen*, it is an error to ignore prior art that lacks test results where performing the idea described in the prior art would result in infringement. Pharmascience submits that even if speculative, Karussis 2006 anticipates the claims of the ‘437 Patent. Pharmascience submits that the statements in Karussis 2006, along with the anticipated PreCISe results to support those statements, are sufficient to meet the disclosure requirement of anticipation.

[478] First, the Court has not ignored Karussis 2006 as prior art; Karussis 2006 has been carefully considered from beginning to end.

[479] Second, I accept the principle set out in *Hospira*, but find that Karussis 2006 is not in the same category of speculative art noted in *Hospira* or *Biogen*.

[480] In *Hospira*, the prior art at issue was the 1994 Kennedy Report, which was intended to “further investigate the tolerability and efficacy of repeated use of [infliximab]…” (at para 68) and which noted that results would be available the following year. In *Biogen*, the anticipatory art at issue was a study protocol, without any results. Karussis 2006 was not a study protocol nor did it set out to investigate any of its suggestions or statements. Karussis 2006 was a report on the discussions of a working group.

[481] In the present case, the idea described in Karussis 2006 is the very idea that Teva was in the process of testing in the PreCISe trial. Karussis 2006 did not set out a study protocol or describe any testing that was in progress or expected results. Karussis 2006 simply suggested

that CIS patients warranted consideration for early treatment. In my view, it would defeat the purpose of clinical trials to support the patentability of an invention (and, of course, its safety and efficacy) if a group of experts could note that a clinical trial conducted by others was in progress and recommend or suggest that what is being tested be done. Moreover, Karussis 2006 did not even recommend that glatiramer acetate be used for CIS patients – only that one of the DMTs approved for RRMS be considered.

[482] I note that Karussis 2006 does not cite the PreCISe trial at all and does not speculate that it would be successful. Statement #5 says only that "there are no data with [Betaseron] or glatiramer acetate in patients with a CIS diagnosis suggestive of MS, although studies are ongoing". The study referred to in the relevant footnote is the CHAMPS study of the interferon Avonex.

[483] Contrary to Pharmascience's submission, Teva was not capitalizing on the Karussis Working Group's ideas, rather it was testing its own idea.

[484] In my view, if Karussis 2006 is anticipatory art, what would prevent a group of experts in any field from having discussions and speculating on the positive outcome of a clinical trial in progress, developed and implemented by others, in order to later argue that their speculation that the trial in progress would be successful anticipated the claims of a patent that are based on such clinical trials. This approach seems to be inconsistent with the objectives of the experimental use exemption established in the common law.

[485] As noted by Teva, the law recognizes that there is no disclosure for the purposes of anticipation where a prior use is experimental (*Bayer Inc v Apotex Inc*, 2016 FC 1013 at paras 157, 162). If a patent cannot be anticipated by its own clinical study, in my view, it cannot be anticipated by the speculative recommendations of a group of experts who discuss the state of MS treatment, note the lack of evidence, and note that trials are underway.

[486] With respect to enablement, I also find that on a balance of probabilities the POSITA could not "work the invention" (*Sanofi* at para 27). While it may appear to be a simple matter to prescribe 20 mg Copaxone for CIS patients given that 20 mg Copaxone was available and was approved for RRMS patients, it was not that simple.

[487] Contrary to Pharmascience's submission – that prescribing an off-label drug was not prohibited and that is all that matters – the POSITA could not have easily prescribed glatiramer acetate (Copoxone 20 mg) to treat a CIS patient.

[488] As noted above, in his oral evidence, Dr. Green stated that prior to November 2007, he and other physicians had prescribed Copaxone 20 mg off-label to treat CIS patients. However, Dr. Green acknowledged that he did not state this in his report on validity.

[489] Dr. Green added that it is common for physicians to prescribe medicines for off-label uses and, in many instances, this may fall within the standard of care.

[490] Dr. Green's evidence is not entirely consistent. His evidence of his own practice varied. His reference to what other physicians did cannot be accepted. He stated that he prescribed 20 mg Copaxone off-label although it was not approved. However, he also stated that he would not have prescribed 40 mg Copaxone based on Pinchasi 2007 because it was not approved. Dr. Green also acknowledged that he was not well versed in the Canadian health system although he had some awareness of national health systems.

[491] I have placed more reliance on Dr. Selchen's opinion, that in his experience CIS patients were not treated with a drug that was not approved for use to treat CIS. He emphasized that a physician would not prescribe a drug for CIS patients in the absence of proof of efficacy. Physicians would use what had a clear evidence base. Dr. Selchen also explained that, practically, he would not have been able to use glatiramer acetate in 2007 as it was not approved and it would not have been covered or reimbursed under any plan. He noted the very high cost of the therapy, which would make it "untenable" to prescribe. Moreover, Dr. Selchen was not aware of other doctors doing so outside of the clinical trial.

[492] I do not find that Dr. Selchen's evidence regarding off-label drugs was inconsistent, as alleged by Pharmascience. Dr. Selchen explained that the reference in a co-authored publication to treating children with glatiramer acetate although off-label was not his area of expertise and that was the input of other authors with expertise in pediatric MS. Dr. Prat later explained that most drugs for children are considered to be off-label because clinical tests of drugs do not engage children for obvious reasons.

[493] Dr. Morrow also stated that off-label drugs would not be prescribed. Contrary to Pharmascience's submission that Dr. Morrow said this could not be "ruled out", her point was that she could not speak for others, as Dr. Green purported to do.

XX. Is the '437 Patent Obvious?

A. *Principles from the Jurisprudence*

[494] The Supreme Court of Canada set out the law on obviousness in *Sanofi.* Subsequent jurisprudence has provided additional guidance on its interpretation and application.

[495] In *Sanofi*, at paras 66-69, the Court followed the approach from *Windsurfing International Inc v Tabur Marine (Great Britain) Ltd*, [1985] RPC 59 (UKCA) as updated in *Pozzoli SPA v BDMO SA*, [2007] FSR 37, [2007] EWCA Civ 588 and described the four steps to guide the analysis of allegations of obviousness:

1. Identify the notional "person skilled in the art" and the relevant common knowledge of the skilled person as of the claim date;

2. Identify the inventive concept of the claim in question or if that cannot readily be done, construe it;

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

4. Determine whether these differences, viewed without any knowledge of the alleged invention as claimed, constitute steps, which would have been obvious to the person skilled in the art or would have required any degree of invention.

[496] The fourth step is referred to as the "obvious to try" test. The Court noted at para 66:

> [66] For a finding that an invention was "obvious to try", there must be evidence to convince a judge on a balance of probabilities that it was more or less self-evident to try to obtain the invention. Mere possibility that something might turn up is not enough.

[497] The Court explained that where the obvious to try test is warranted, other factors may assist and inform that step. The Court noted, at paras 69-71, that the relevant factors vary with the circumstances and would include:

- "Is it more or less self-evident that what is being tried ought to work? Are there a finite number of identified predictable solutions known to persons skilled in the art?"

- "What is the extent, nature and amount of effort required to achieve the invention? Are routine trials carried out or is the experimentation prolonged and arduous, such that the trials would not be considered routine?"

- "Is there a motive provided in the prior art to find the solution the patent addresses?"

- The course of conduct leading to the invention, including the history of the invention, whether the inventor arrived at the invention quickly and easily based on the prior art and common general knowledge, and the inventors' particular expertise compared to that of the POSITA.

[498] In *Pfizer Canada Inc v Apotex Inc*, 2009 FCA 8 at para 29, the Court of Appeal clarified that "obvious" within the meaning of "obvious to try" means "very plain" and that possibility and speculation is not the test, nor is "worth a try"; rather, the invention must be "more or less self-evident", as noted in *Sanofi*.

[499] In *Ciba Specialty Chemicals Water Treatments Limited's v SNF Inc*, 2017 FCA 225 at para 62 [*Ciba*], the Court of Appeal noted that, in bridging the differences between the invention and the prior art, "[t]he Skilled Person can have recourse to their common general knowledge supplemented by those pieces of prior art which could be discovered by a reasonably diligent search".

[500] In *Hospira*, the Court of Appeal clarified the distinction between the obvious to try test (step 4) and the factors that inform it, at para 90:

> [90] It should be noted that, whereas being "more or less self-evident to try to obtain the invention" (per *Sanofi* at para. 66) is a

> requirement for obviousness to try, being "more or less self-evident that what is being tried ought to work" (per *Sanofi* at para. 69) is not a requirement but merely a factor to be considered

[501] In *Hospira*, the Court also considered the scope of the prior art that is relevant for the obviousness analysis, noting that at the obvious to try step, the fact that a prior art reference would not turn up or be part of a mosaic is relevant. The Court of Appeal noted at para 86:

> [86] In light of section 28.3 of the *Patent Act* and the applicable jurisprudence and commentaries, I conclude that it is an error to exclude from consideration prior art that was available to the public at the relevant date simply because it would not have been located in a reasonably diligent search. The likelihood that a prior art reference would not have been located by a PSA may be relevant to consideration of step 4 of the obviousness analysis (whether differences between the state of the art and the inventive concept constitute steps which would have been obvious to the PSA) in that the uninventive PSA might not have thought to combine that prior art reference with other prior art to make the claimed invention. However, excluding prior art simply because it is difficult to find is problematic because it would result in the possibility of a valid patent on an invention that had, but for some non-inventive tweak, already been disclosed to the public. In my view, that is not what Canada's patent regime is intended to permit.

[502] Unlike anticipation, the analysis required to determine obviousness does not focus on a single piece of prior art. For obviousness, the question is whether the POSITA, relying on all the relevant prior art and with the common general knowledge supplemented by information that could be discovered by a reasonably diligent search, would reach the invention directly and without difficulty or whether inventive ingenuity would be required.

[503] In *Tearlab* at paras 73 and 81, the Court of Appeal explained how prior art is used differently in assessing allegations of anticipation and obviousness, noting at para 73:

> [73] …There is nothing "contradictory" in finding that a prior art reference, when considered alone, does not anticipate, but that it can nonetheless render a claim obvious when combined with another reference.

[504] At para 81, the Court of Appeal elaborated:

> [81] . . . Every element of an obvious claim need not be found in single prior art reference; that is the test for anticipation. The test is rather whether a POSITA can bridge the gap between the state of the art at the relevant time and the claim as construed, without inventive ingenuity. Prior art will be used in the application of both anticipation and obviousness, but in a different manner; anticipation will be established if a single document can be found which gives a POSITA all the information which is needed to produce the claimed invention without the exercise of any inventive skill, whereas for obviousness it is the cumulative effect of the prior art that must be considered to determine whether the skilled but unimaginative technician would have come to the solution taught by the patent directly and without difficulty. As stated by Harold G. Fox in his seminal book titled *Canadian Patent Law and Practice*, 4th ed. (Toronto, Ontario: Carswell, 1969), at p. 137:
>
> > . . . Prior specifications are generally used to show anticipation if they disclose exactly and fully what the patentee has claimed. If such disclosure is not made by the prior specification and it cannot be used as an anticipation, it may be used as indicating the state of the art at the time that the patentee made his alleged invention and as showing that what the patentee did was so slight a contribution to existing knowledge as to lack the essential element of invention and to be merely obvious…

B. *Pharmascience's Submissions*

[505] Pharmascience submits that the subject matter of the claims reflected the state of the art in November 2007; there were no differences and no inventive ingenuity was required to reach the subject matter of the claims.

[506] As repeatedly noted, Pharmascience interprets the claims of the '437 Patent more broadly than the Court's construction, but submits that regardless, the claims are obvious.

[507] Pharmascience argues that for single attack patients who have been diagnosed pursuant to the McDonald criteria with MS, there are no differences between the state of the art and the subject matter of the claims. As Pharmascience notes, Copaxone was being used to treat RRMS patients well before November 2007. Pharmascience also points to Pinchasi 2007, which disclosed the use of 40 mg glatiramer acetate for RRMS. If Pharmascience's broader interpretation of the claims had prevailed, the validity attack would succeed.

[508] Pharmascience also argues that if the claims are restricted to single attack patients who do not meet the MS diagnosis based on the McDonald criteria (as the Court has construed the claims), there are still no differences between the state of the art and the subject matter of the claims. Pharmascience relies on the recommendations in Karussis 2006, other prior art, and the common general knowledge, including the knowledge that the PreCISe trial of glatiramer acetate for CIS patients was ongoing and expected to be successful. Pharmascience points to the evidence of Teva's witness, Dr. Day, in support of this expectation of success.

[509] Pharmascience submits that the following information was known and reflects that state of the art as of November 2007:

- Over 80% of single-attack patients with MRI lesions go on to develop MS and that single-attack patients with T2 lesions on MRI were considered to already have MS;

- Canadian and international guidelines noted the need to use DMTs early in the disease course of RRMS;

- Karussis 2006 recommended that glatiramer acetate be used to treat single-attack patients who satisfied the McDonald criteria for MS;

- The prevailing view of MS experts was that earlier treatment, at the time of the first attack, was preferable;

- Four first-line DMTs were available for RRMS; three interferon products (Avonex, Betaseron and Rebif) and glatiramer acetate (Copaxone);

- The interferon products (Avonex, Betaseron and Rebif) had been tested in Phase III clinical trials (the CHAMPS, ETOMS and BENEFIT trials) and were demonstrated to be effective in treating CIS patients;

- Karussis 2006 recommended that glatiramer acetate also be used to treat single-attack patients who fell short of the McDonald criteria for a diagnosis of MS;

- It was known that the PreCISe trial – a phase III clinical trial assessing the effectiveness of glatiramer acetate in treating CIS patients – was underway; and,

- Karussis 2006 reported that a clinical trial of glatiramer acetate in CIS patients was underway and "should work". Pharmascience suggests that this is a reference to the PreCISe trial. Pharmascience also relies on Panitch 2007, a commentary reporting on the BENEFIT trial of Betaseron, an interferon, where the author stated that the PreCISe trial was "likely to show a comparable magnitude of clinical efficacy".

[510] With respect to Teva's argument that the '437 Patent disclosed results not expected and not disclosed in any prior art, such as a 50% reduction in new T2-weighted lesions, Pharmascience submits that even if this result was unexpected, the invention was still obvious. Pharmascience submits that if it were obvious to try to use glatiramer acetate for single attack patients, the "golden bonus" that this reduced lesions by 50% does not make it inventive (*Janssen Inc v Teva Canada Limited*, 2015 FC 184 at para 100 [*Janssen*]).

[511] Pharmascience further argues that the claimed 50% reduction (in claim 33) was not an unexpected result for the treatment of a single attack patient. Pharmascience relies on the results of the use of glatiramer acetate in RRMS patients and the results of the ETOMS, CHAMPS and

BENEFIT trials regarding the use of interferons in CIS patients that showed significant reductions in lesions.

[512] Pharmascience submits that the threshold of obviousness does not require the results of clinical trials.

[513] Pharmascience argues that if there were any differences between the state of the art and the subject matter of the claims, the gap could be bridged by the POSITA using their common general knowledge and additional information found by way of a reasonably diligent search.

[514] Pharmascience submits that it was common general knowledge that interferons had been demonstrated to be effective in treating CIS patients; Karussis 2006 recommended that glatiramer acetate be considered and that it should be effective; and, the PreCISe trial was underway and would not have been undertaken without an expectation of success.

[515] Pharmascience submits that the POSITA would be motivated to look for other treatments and the only other treatment available at that time was glatiramer acetate for RRMS. Pharmascience adds that even though treatment of CIS patients with glatiramer acetate was not yet approved in 2007, some physicians prescribed it.

[516] Pharmascience submits that the evidence of Teva's witness, Dr. Selchen, on obviousness should be ignored for several reasons.

[517] Pharmascience first suggests that Dr. Selchen was misinstructed regarding the *Sanofi* test. Pharmascience submits that Dr. Selchen erroneously opined on whether it was self evident that what is being tried would succeed, which is a factor in the obvious to try test, not the test itself *(Hospira* at para 90). Pharmascience also submits that Dr. Selchen erred by failing to consider that any differences between the state of the art and the invention could be bridged, not only with common knowledge, but with the results of information obtained by a reasonably diligent search.

[518] Second, Pharmascience characterizes Dr. Selchen as a sceptic who did not demonstrate a mind willing to understand. Pharmascience points to *Biogen* at para 170, where the Court noted "the prior art should be approached by a motivated POSITA with a mind willing to understand, not one myopically focused on seeking out failure."

[519] Third, Pharmascience suggests that Dr. Selchen's evidence about off-label drugs was inconsistent. Pharmascience points to Dr. Selchen's acknowledgment that an article he co-authored referred to the treatment of children with glatiramer acetate, which would be off-label. Pharmascience suggests that if children could be treated off label, then there should have been no reason not to treat CIS patients off-label with glatiramer acetate.

[520] Pharmascience also argues that the Court should draw an adverse inference from Teva's failure to provide any evidence from the inventors of the '437 Patent, who are still alive and could have been contacted. Pharmascience submits that the evidence proffered by Teva from Dr. Kreitman does not address the work involved in the invention. Pharmascience submits that the Court should infer that Teva conducted the PreCISe trial only to confirm what was already

known and obvious – that glatiramer acetate would work better if administered earlier to CIS patients.

C. *Teva's Submissions*

[521] Teva notes that obviousness is a difficult test to meet and submits that Pharmascience has not established that the POSITA would have come directly and without difficulty to the subject matter of the claims (citing *Beloit v Valmet Oy* (1986), 8 CPR (3d) 289 (FCA) at para 294).

[522] Teva submits that Pharmascience relies on hindsight analysis. What may appear to be obvious today based on results later observed or demonstrated, such as in the PreCISe trial, is not the issue, rather whether it was obvious in 2007.

[523] Teva does not fully agree with Pharmascience's description of the state of the art or the common general knowledge. Teva submits that, in November 2007, the early treatment of CIS patients was not part of the common general knowledge. There remained a debate on whether early treatment with any DMTs should be pursued. Teva notes that Dr. Green stated that there was an "emerging consensus" for early treatment in 2007 but in the U.K. litigation, he acknowledged that there were two schools of thought. Teva notes that Dr. Green failed to mention that some experts in the field had reservations about treating patients that had not been diagnosed with MS.

[524] Teva acknowledges that it was generally known that the PreCISe trial was underway. However, Teva again notes that, as of November 2007, glatiramer acetate was not a viable treatment option for CIS; there was no evidence of any type (i.e., no clinical studies with reported class I, II, III or IV evidence) that glatiramer acetate would be therapeutically effective for treatment of CIS. In addition, there was not even any speculation that it would be effective to reduce progression of MRI-monitored disease activity, reduce progression of symptoms of MS prior to the development of CDMS, reduce the frequency of relapse, or reduce new T2-weighted lesions by at least 50%.

[525] Teva acknowledges that, as of November 2007, interferon therapies were known and were approved for treating CIS patients but submits that interferons are different compounds.

[526] Teva submits that Karussis 2006 was not common general knowledge. Teva also cautions against reliance on more obscure articles, which were not identified in the prior art, and on stray references in footnotes from co-authored papers that were not directly referred to by the expert.

[527] Teva submits that Dr. Green relied on passages of Karussis 2006 without considering its whole context, in particular that Karussis 2006 accepted that the recommendation for early treatment of CIS patients was not evidence based. Teva submits that neither Karussis 2006 nor Panitch 2007, relied on by Dr. Green, refer to any evidence that glatiramer acetate would be effective for CIS patients.

[528] Teva acknowledges that Kappos 2006, referred to by Dr. Green and Dr. Selchen, disclosed that earlier treatment is better than later treatment as the disease progresses. Teva notes, however, that this disclosure is based on treatment with Betaseron and not with glatiramer acetate. Teva submits that no inferences about glatiramer acetate can be drawn from interferons.

[529] Teva submits that there were substantial differences between the state of the art and the subject matter of the claims.

[530] Teva argues that bridging the differences between the state of the art, which did not support the use of glatiramer acetate for CIS patients, and the subject matter of the claims required inventive ingenuity. Inventiveness was required because there was a debate about whether to even treat CIS before a confirmed MS diagnosis; other proven and approved therapies for CIS (e.g., interferons) were available and would have been the "go to" if treatment were pursued; and, there was no evidence of the efficacy of glatiramer acetate to treat CIS.

[531] Teva submits that the invention was not obvious to try, noting that the "mere possibility that something might turn up is not enough" (*Sanofi* at para 66).

[532] According to Teva, viewed without knowledge of the invention as disclosed and claimed in the '437 Patent, the POSITA would not have expected the outcomes claimed, in particular, that treating CIS patients with glatiramer acetate would lead to a 50% reduction in new T2 lesions, noting that this result was greater than any trial results of previous CIS therapies. Teva adds that it was not self-evident that glatiramer acetate would be effective in treating CIS, or that

it would achieve this 50% reduction in new T2 lesions. Testing was required and had not been completed. In addition, the POSITA would not expect the therapeutic benefits of the PreCISe trial simply because the PreCISe trial was underway.

[533] Teva disputes Pharmascience's characterization of Dr. Day's evidence, noting that Dr. Day did not say that it was more likely than not that a Phase III clinical trial would succeed. Rather, Dr. Day stated that this would depend on the work done before Phase III. Teva notes that there were no predecessor Phase II studies, pilot studies or even case reports for glatiramer acetate for CIS patients.

[534] Teva also disputes that Dr. Selchen was not properly instructed with respect to the test for obviousness, noting that he was guided by the S*anofi test.* Teva submits that the excerpts of Dr. Selchen's testimony that Pharmascience relies on were Dr. Selchen's comments in response to Dr. Green, not Dr. Selchen's full assessment of the obvious to try test.

[535] Teva argues that the POSITA would not have been motivated to use unapproved therapies for CIS adding that off label use would not be possible.

[536] With respect to Pharmascience's submissions on the "non-invention" story, Teva points to its evidence regarding the trial protocols and the extensive planning and investment that are required and to Dr. Kreitman's evidence regarding the PreCISe trial in particular.

[537] Teva argues that it invested resources, expertise and ingenuity to bring about the invention, noting that the clinical trial was a large Phase III study. Without the results of the PreCISe trial, the POSITA would not be aware of the benefits of glatiramer acetate for CIS patients.

D. *What do the Experts Say?*

(1) Dr. Green

[538] Dr. Green stated that there was no difference between the state of the art as of November 2007 (i.e., the starting point) and the subject matter of the claims of the '437 Patent (i.e., the end point). He explained that the state of the art had already reached the point that glatiramer acetate was being used to treat CIS patients in large clinical studies and that the "consensus view" was that treating CIS patients with glatiramer acetate was a reasonable approach, glatiramer acetate should work to treat CIS patients; and the PreCISe trial was likely to show that treatment at the time of the initial CIS would have enhanced efficacy compared to later treatment of RRMS (again relying on Karussis 2006).

[539] Dr. Green noted that the POSITA was well aware of the concept of CIS. In addition, the POSITA knew that the interferons that had been effectively used to treat MS had been shown to be effective in treating CIS patients. Dr. Green expressed the view that the POSITA would understand that these drugs worked the same way in CIS patients as in MS patients, only they were administered at an earlier stage. In Dr. Green's view, this knowledge, along with the

knowledge of the prior art that showed the effectiveness of glatiramer acetate for RRMS, and that the PreCISe trial was already in progress, would lead to the view that glatiramer acetate would also be expected to work for CIS patients.

[540] Dr. Green noted that Phase III clinical trials are designed to provide clinically and statistically significant evidence of efficacy and safety to regulatory authorities to obtain marketing approval. He added that these studies, such as the PreCISe trial, are not undertaken by pharmaceutical manufacturers without a confident expectation of success.

[541] Dr. Green stated that this would have been self-evident to the POSITA that this treatment would be effective given the ongoing PreCISe trial, which was comparing the administration of glatiramer acetate and a placebo to CIS patients. This knowledge would have been combined with the conclusions from Karussis 2006 that glatiramer acetate should work and the other art that supported early treatment of CIS patients.

[542] In Dr. Green's view, the POSITA would have been familiar with the clinical study design required to qualitatively and quantitatively assess and measure glatiramer acetate's effect on reducing the likelihood of progression to CDMS and/or delaying the progression to CDMS in CIS patients.

[543] Dr. Green explained that the POSITA would have been motivated to find new therapies for CIS for many reasons, including because the approved products were all interferons. If a patient could not tolerate an interferon, an alternative therapy would be desirable. Dr. Green

explained that the natural choice would be the safe and well tolerated therapies that were used to treat RRMS in the approved doses of 20 mg or 40 mg.

[544] Administering glatiramer acetate to CIS patients and confirming its efficacy would be a matter of simply prescribing glatiramer acetate, which was an existing, approved medication (Copaxone), to CIS patients and monitoring their progression. Doing so would not have required any significant effort beyond the normal, routine work of a clinician.

[545] As noted above with respect to anticipation, on cross-examination, Dr. Green acknowledged that Karussis 2006 referred to the available DMTs, not specifically glatiramer acetate, that the clinical trials were underway but not completed, and that there was no data regarding the effectiveness of glatiramer acetate for CIS, only for RRMS.

[546] With respect to Dr. Green's view that in November 2007 there was an "emerging consensus" regarding early treatment, on cross-examination, Dr. Green agreed that a subset of experts questioned this approach.

[547] Counsel for Teva noted that in the U.K. litigation, Dr. Green referred to the two schools of thought, not an emerging consensus, as he now states. Dr. Green explained that his statement regarding the consensus view remains true and the debate was about who warranted early treatment. Dr. Green added that early treatment was being recommended by the medical advisory board of the National MS Society of the U.S. and others. He reiterated his opinion that "[i]t was

recognized that the benefits of early treatment generally would outweigh the costs and side effects in the aggregate for patients who had a CIS".

[548] Dr. Green acknowledged that the studies he relied on regarding glatiramer acetate were with respect to MS or RRMS patients, not CIS patients. He noted that Comi 2001 studied RRMS patients and reported a 31% reduction in new T2 lesions (not a 50% reduction as claimed in claim 33 of the '437 Patent).

[549] Counsel for Teva sought to have Dr. Green acknowledge that no data existed in November 2007 to show that any drug reduced new T2 lesions by at least 50%. Counsel pointed Dr. Green to his own publication (2006) which reported that 20 mg glatiramer acetate decreased the rate of relapses and new MRI lesions by approximately 30%. Dr. Green agreed that this was consistent with the Comi 2001 study.

[550] With respect to the PreCISe trial, in progress in 2007, Dr. Green noted that it was well known and well publicized by Teva and there was an "extraordinarily high likelihood that [glatiramer acetate] was going to work". He added that the "field" was anticipating a result that would show efficacy similar to the therapies that existed to that date.

[551] On cross-examination, Dr. Green acknowledged that whether a treatment is effective is not known on a patient-by-patient basis; rather that such knowledge is based on clinical trials in populations of patients and from clinical experience.

(2) Dr. Selchen

[552] In Dr. Selchen's view, there were differences between the state of the art in 2007 and the claims of the '437 Patent. He noted that while the claims of the '437 Patent are based on the results of the PreCISe trial, which provided evidence that glatiramer acetate is effective to treat CIS patients, the state of the art in 2007 did not include evidence that glatiramer acetate had been used to treat CIS patients or that it was effective, even in uncontrolled studies or patient case reports.

[553] Dr. Selchen agreed that the POSITA would understand that the Canadian and international guidelines noted the need to start treatment with interferons or glatiramer acetate early in the course of the disease for RRMS to treat "disease progression", i.e., including the reduction in frequency and relapse of MRI lesions. Dr. Selchen noted, however, that there was some controversy about what "early" meant. As noted above with respect to anticipation, Dr. Selchen noted the two schools of thought regarding early treatment.

[554] Dr. Selchen strongly disagreed that there was any consensus that treatment with glatiramer acetate would show enhanced efficacy for CIS patients compared to RRMS. He noted that Dr. Green's reference to a "consensus view" was likely a reference to Karussis 2006; a single paper that was not evidence based.

[555] Dr. Selchen agreed, as noted with respect to the allegations of anticipation, that it would have been reasonable to *consider* glatiramer acetate as an option for CIS, but there were other offsetting considerations, including the availability of approved alternative DMTs (i.e.,

interferons), the inability to prescribe glatiramer acetate due to the lack of regulatory approval and reimbursement and the lack of any data on efficacy.

[556] Dr. Selchen agreed that Rebif, an interferon, which was approved for RRMS on a three times per week dosage regimen, was shown to have delayed the onset of CDMS in the ETOMS study. Dr. Selchen also agreed that the once-a-week Rebif drug had been shown to significantly reduced disease activity in CIS patients, although it had no effect on RRMS.

[557] Dr. Selchen did not agree that Comi 2006 made any conclusions about early treatment for CIS, only for RRMS. Dr. Selchen did not accept the proposition that Comi 2006 concluded that there would be a greater benefit for treatment for CIS patients than RRMS patients.

[558] Dr. Selchen acknowledged that Kappos 2006, that reported on the BENEFIT study (of Betaseron), concluded that treatment earlier in the disease is more effective than later. In Dr. Selchen's opinion, this was a general hypothesis based on only a trend in the data. Dr. Selchen stated that he was "not suggesting that there is no merit in the argument that early treatment is better than later treatment. In 2020 we know this is true". However, he explained that observing a trend is not evidence.

[559] Dr. Selchen also acknowledged that Panitch 2007 opined that the results of the PreCISe trial were likely to be similar to the results of the BENEFIT trial, but noted that Panitch also recommended waiting for the McDonald criteria to be established (i.e., a diagnosis of MS) before commencing treatment.

[560] Dr. Selchen also disagreed with Dr. Green that it would have been self-evident to the POSITA to look to glatiramer acetate to treat CIS because a clinical trial was underway.

[561] Dr. Selchen noted that predicting the outcome of a clinical study in progress is difficult. He opined that the POSITA would not have had a high degree of confidence that glatiramer acetate would be useful to treat CIS, nor confidence that it would be more effective than existing therapies (the interferons) or more effective than glatiramer acetate in RRMS patients.

[562] Dr. Selchen explained that arriving at the claimed subject matter required a clinical trial – which is not something that a POSITA could do. Dr. Selchen stated that the design and successful conduct of the PreCISe trial (or a similar trial) would have required both expertise and ingenuity that went beyond routine work and the capabilities of the POSITA.

[563] Dr. Selchen stated that, although a clinician could have considered glatiramer acetate for their CIS patients, they would not have been motivated to do so, because there was no evidence of any efficacy; other proven and approved therapies were available, which would have been substantially reimbursed by most drug plans; there was debate within the field regarding whether to treat CIS before a confirmed MS diagnosis; and, the success of the ongoing study was uncertain. As a result, it would have been prudent to wait for the results and prescribe based on scientific evidence.

E. *The Claims of the ‘437 Patent are Obvious*

[564] As found above, the claims of the ‘437 Patent address a patient who has had a single clinical attack, i.e., a CIS patient – not a patient who has been diagnosed with MS pursuant to the McDonald criteria.

[565] The *Sanofi* test guides the analysis of whether the claims of the ‘437 Patent are obvious.

[566] As noted in *Tearlab* at para 73, it is not contradictory to find that a prior art reference, such as Karussis 2006, when considered alone, does not anticipate, but when such a reference is considered in combination with other references, it can make a claim obvious.

[567] The Court of Appeal noted, at para 81 that “the test [for obviousness] is rather whether a POSITA can bridge the gap between the state of the art at the relevant time and the claim as construed, without inventive ingenuity”. The Court added that, “for obviousness it is the cumulative effect of the prior art that must be considered to determine whether the skilled but unimaginative technician would have come to the solution taught by the patent directly and without difficulty”.

[568] The POSITA is described above and, more generally, is a practicing neurologist with knowledge of MS and experience treating MS patients.

[569] The inventive concept is the subject matter of the claims. The invention generally claims the use of glatiramer acetate for use in delaying the onset of CDMS in CIS patents at risk of developing CDMS and before its onset.

(1) The State of the Art

[570] In some respsects, Pharmascience's description overstates the state of the art. However, Pharmascience's overall characterization of the state of the art is supported by the evidence.

[571] There is no dispute that approximately 80% of CIS patients with lesions go on to develop MS. Dr. Selchen initially stated that 30-70% do not, but ultimately agreed with the statement that 80% do develop MS, as the '437 Patent also states.

[572] While it is an exaggeration to state that there was a strong consensus that early treatment of CIS patients should be pursued, the evidence supports that this was the prevailing view as of November 2007. As Dr. Green indicated, while a subset of experts did not share this view, the National MS Society in the U.S. recommended early treatment. Dr. Green's opinion was that it was recognized that the benefits of early treatment would outweigh the costs and side effects "in the aggregate" for CIS patients.

[573] Although Dr. Selchen did not agree that this was the prevailing view, he did agree that the statement in Karussis 2006 – that early treatment warranted consideration – was not

controversial. As noted above, while Karussis is not common general knowledge, the authors referred to several studies that were prior art and/or common general knowledge.

[574] The preponderance of evidence supports the view that the state of the art recognized the benefits of early treatment of CIS patients. In addition, the prior art that reports extensively on the CHAMPS, ETOMS and BENEFIT Phase III clinical trials of the interferon DMTs all noted positive results and recommended early treatment of CIS patients.

[575] The prior art notes the results of the use of DMTs for RRMS and the results of the use of interferons for CIS. The reports regarding the studies of the interferons appear to make more general statements about the benefits of early treatment. Clearly, the state of the art, even before 2007, was that early treatment was being considered and, in some cases, pursued for CIS patients.

[576] For example, Filippi 1994 reported on a 5-year study that assessed the likelihood of a CIS patient developing MS within 5 years. It demonstrated that, for patients who had a clinical episode suggestive of a demyelinating attack with brain lesions (i.e., patients with a CIS suggestive of MS), progression to MS occurred in 65% of those patients within 5 years. As noted by the experts, the estimate in 2007 was that 80% of CIS patients developed MS, although the length of time for this to occur was not specified.

[577] Comi 2001 noted that the ETOMS Phase III clinical trial reported that the use of Rebif reduced the proportion of CIS patients who developed CDMS and reduced the frequency of relapses.

[578] Comi 2006 supported early treatment of MS. Among other things, Comi 2006 discussed the CHAMPS and ETOMS trial results and concluded that "[the available] data [with respect to interferons] suggest that early treatment of MS patients with immunomodulatory drugs is advisable."

[579] Kappos 2006 reported the results of the BENEFIT trial that studied the use of Betaseron every other day in CIS patients. Among other things, the results of the trial showed a 50% risk reduction for progression to CDMS for CIS patients treated with Betaseron compared to placebo. It also showed a 33% reduction in the mean number of T2 lesions. As noted above, Dr. Selchen regarded Kappos' findings as based only on a trend in the data. However, other reports on the BENEFIT trial supported the conclusion that it showed the advantages of early treatment.

[580] Frohman 2006 also noted the results of the ETOMS and CHAMPS trials and set out arguments in favour of early treatment of MS, including for CIS patients.

[581] Thrower 2007 reviewed the CHAMPS, CHAMPIONS (an extension of CHAMPS), ETOMS, and BENEFIT clinical trials, all of which investigated the use of DMTs in treating high-risk CIS patients. The author concluded that early treatment should be considered for CIS patients who are at high risk for progression to CDMS.

[582] Panitch 2007 is a short commentary on the BENEFIT trial. Dr. Panitch commented that the BENEFIT trial represented the third trial (the others being CHAMPS and ETOMS) to show "essentially the same outcome" (i.e., effective treatment) of CIS patients. Panitch noted that "a similar large study of glatiramer acetate versus placebo, given the acronym PRECISE, is currently in progress and is likely to show a comparable magnitude of clinical efficacy."

[583] Dr. Selchen expressed the view that Panitch's comment about a "comparable magnitude of clinical efficiency" related to the previous sentence where Panitch noted that an additional feature of the BENEFIT trial showed a "clinically unimpressive result", and that Panitch was suggesting that PreCISe would also show a clinically unimpressive result. However, Dr. Selchen's interpretation is not borne out when the full paragraph is read. Panitch was referring to the positive results of the BENEFIT study overall, noting that its primary outcome was similar to that of CHAMPS and ETOMS.

[584] As noted above, Pharmascience and Dr. Green overstated Karussis 2006. Karussis did not recommend glatiramer acetate specifically, nor did it point to any evidence of its efficacy. However, Karussis 2006 did draw on the prior art to suggest that early treatment of CIS patients warranted consideration.

[585] Karussis 2006 stated the approved DMTs should work based on studies for RRMS. Karussis did not state that the PreCISe trial should work. The reference in Karussis 2006 to a clinical trial in progress was a reference to CHAMPS. Although Dr. Selchen agreed on cross-

examination that “presumably” Karussis was referring to the PreCISe trial, this presumption is not accurate as Dr. Selchen was not directed to the footnote for that statement.

[586] With respect to the reliance on the studies done on the treatment of CIS patients with interferons, both Dr. Selchen and Dr. Prat stated that no inferences could be drawn from the interferons with respect to glatiramer acetate due to their different mechanism of action. These different mechanisms were not explained. However, all the experts agreed that interferons were different compounds from glatiramer acetate.

[587] Dr. Green’s opinion was not based on an assumption that because interferons worked for CIS patients, glatiramer acetate would also work. Dr. Green acknowledged that interferons were different. Rather, his opinion was that if interferons worked for RRMS patients and also showed positive results for CIS patients, a similar outcome would be expected for glatiramer acetate, which had also been demonstrated to be effective for RRMS patients. The point is that the glatiramer acetate treatment should begin earlier, not that it should work in the same way as the interferons.

(2) The Differences between the State of the Art and the Subject Matter of the Claims

[588] The state of the art in November 2007 was that DMTs (interferons and glatiramer acetate) worked for RRMS; interferons had been demonstrated to be effective for CIS patients; there remained a debate about early treatment, but the prevailing view was that early treatment was

preferable; and, there was no evidence that glatiramer acetate would be effective for CIS patients, although it was known that the PreCISe trial was in progress.

[589] As noted, the invention generally claims the use of glatiramer acetate for use in delaying the onset of CDMS in CIS patents at risk of developing CDMS and sets out more specific outcomes and how it is administered (by injection, daily, 20 mg or 40 mg).

[590] The difference between the state of the art and the subject matter of the claims is that state of the art did not include clinical studies to demonstrate that glatiramer acetate administered to CIS patients was effective to delay the onset of CDMS (or MS) or to achieve the other therapeutic benefits and specific outcomes.

(a) *Obvious to try*

[591] The issue is whether it would have been obvious to the POSITA to administer glatiramer acetate to CIS patients to delay the onset of CDMS (or MS). Would the unimaginative but skilled POSITA come to the solution taught by the patent directly and without difficulty?

[592] In my view, the evidence shows that on a balance of probabilities it was obvious to try to obtain the invention. It was more or less self-evident to do so. It would not have required much, if any, imagination for the POSITA to look to glatiramer acetate for the treatment of CIS patients to delay the onset of MS and reduce the frequency of relapses, among other benefits. It was more than a mere possibility that this would be an effective treatment, given that approximately 80%

of CIS patients go on to develop MS and that glatiramer acetate was proven effective for RRMS. It was more than simply “worth a try”.

[593] Dr. Selchen’s opinion that the invention was not self-evident appears to conflate the obvious to try test with the factor or consideration that informs the test, i.e., whether it was self-evident that it would work, in the sense of being effective for CIS patients to delay the onset of MS and achieve the other claimed benefits. In any event, it is the Court that must determine whether the invention was obvious to try. As with many legal tests guided by factors, it can be somewhat circuitous to ask whether it is obvious to try to obtain the invention then to also consider whether it was obvious that the invention would work. Regardless, the relevant factors and the evidence supports that it was obvious to try.

[594] Teva’s submission – that the therapeutic benefits or outcomes of the ‘437 Patent were not obvious or expected – does not diminish that the invention was obvious to try. In *Janssen* at para 100, the Court explained, that “if a patentee obtains a workable formulation, the later discovery of one of its inherent characteristics does not add anything inventive to what had already been discovered: see *Alcon Canada Inc. v Apotex Inc*., 2012 FC 410 at para 45, [2012] FCJ No 1707 (QL).” In the present circumstances, once the POSITA pursued the use of glatiramer acetate for CIS patients, the claimed benefits would follow.

(b) *The relevant factors*

[595] With respect to the relevant factors, it was not self-evident that treating CIS patients with glatiramer acetate would work, in the sense of achieving reductions in relapses, reducing MRI lesions and, more generally, delaying the onset of MS. However, as noted above, the results of glatiramer acetate for RRMS patients had been demonstrated, early treatment was a prevailing or trending view, there appeared to be no strong evidence suggesting that early treatment would be harmful, and to the extent that the POSITA would be influenced by the results of the clinical trials of the interferons, the administration of glatiramer acetate would be an option. The only other solution to the treatment of CIS was, as noted, the administration of the approved interferons. There is no evidence that other therapies – apart from glatiramer acetate – were alternatives. Nor is there evidence of other approaches to treat CIS patients.

[596] It would not have required significant effort to achieve the invention because glatiramer acetate (Copaxone) was well known, approved for the treatment of RRMS, and available. Although the evidence is mixed regarding off-label use of drugs, it would be theoretically possible for the POSITA to administer glatiramer acetate in the 20 mg dose and monitor the patient regularly. While a clinical trial would not be routine for the POSITA, as it requires planning, special expertise, funding and time, a clinical trial would not be otherwise arduous, Copaxone was available and there was no need for further experiments with respect to its formulation, administration or dosing regimen.

[597] There was also a motive to pursue glatiramer acetate for CIS patients. As noted by Dr. Green, if the CIS patient cannot tolerate an interferon or experiences adverse side effects, the only other option would be glatiramer acetate, which was a well-known DMT. More generally, the state of the art supports an overall motive to pursue early treatment of CIS patients.

[598] With respect to the course of conduct of the inventors, there is no first hand evidence. However, an adverse inference, as suggested by Pharmascience, that Teva was merely confirming what was known, is not warranted. Dr. Kreitman described the phase III clinical trial (the PreCISe trial) as a placebo-controlled, randomized, double-blind, multicenter trial with an additional 2 year open-label phase during which all participants would receive Copaxone 20 mg daily. There were 481 patients in the study, which occurred in 80 sites in 16 countries. Dr. Kreitman stated that the study demonstrated that 20 mg daily glatiramer acetate was efficacious in delaying the onset of CDMS in CIS patients.

[599] Teva was not simply confirming what was known, because it was not a certainty in 2007 that glatiramer acetate would be effective for CIS patients. Regardless, this factor is not sufficient to overcome the other factors that support the conclusion that it was obvious to try.

[600] In conclusion, the ‘437 Patent is not anticipated by Karussis 2006, but is obvious.

XXI. The ‘802 Patent

[601] The description of the ‘802 Patent is set out above in Part XI.

A. *The POSITA for the '802 Patent*

[602] Teva submits that the experts agreed that the POSITA includes a neurologist with experience understanding the results of clinical studies. Teva disputes Pharmascience's submission that the POSITA includes a member of a drug development team.

[603] Dr. Green described the POSITA in the same way as he did with respect to the '437 Patent.

[604] Dr. Prat described the POSITA as including a doctor who treats MS, likely a neurologist with a specialty in MS. Dr. Prat generally agreed with Dr. Green regarding the attributes of the POSITA. However, Dr. Prat did not share Dr. Green's view that the POSITA would necessarily have experience with the design of studies required for drug development. He noted that the POSITA may have experience with participation in clinical studies focusing on MS but not in their design, as that is typically the expertise of another type of specialist.

[605] Dr. Vosoughi described the POSITA as including a doctor specializing in neurology with several years of experience treating patients with MS.

[606] In my view, the POSITA for the '802 Patent is the same as for the '437 Patent; a practicing neurologist with several years of experience evaluating, diagnosing and treating patients with MS. This POSITA would be familiar with therapeutic agents available for the treatment of MS (i.e., DMTs), their dosing schedules and side effects or adverse events that

occur with the various DMTs. The POSITA would have some knowledge of and familiarity with clinical studies and their interpretation, but would not be a member of a drug development team.

B. *The Construction of the Claims of the '802 Patent*

[607] There is no dispute regarding the construction of the claims. All the experts agree that the claims address the use of 40 mg of glatiramer acetate, administered by subcutaneous injection three times per week (and with a day in between injections), for the treatment of patients with RRMS.

[608] Claims 36 to 39, 48 and 53 claim treatment effects such as reducing the frequency of relapses, the number of enhancing T1 lesions, the mean number of new T2 lesions and the level of disability measured in different ways.

[609] Claims 47 and 54 to 57 specify tolerability effects compared to 20 mg daily, such as reducing the frequency of immediate post injection reactions or of injection site reactions (claims 47, 54 and 55) and specific injection site reactions (e.g., pain or welt) (claim 57).

XXII. Prior Art and Common General Knowledge related to the '802 Patent

[610] The common general knowledge as of August 2009 builds on that set out above with respect to the '437 Patent. There is no dispute that as of August 2009, the POSITA was aware of the characteristics of MS, the types of MS, including RRMS, the diagnostic criteria, and the

DMTs (interferons and glatiramer acetate) available for MS. In addition, by August 2009, Copaxone 20 mg administered by injection daily for CIS was available.

[611] However, not all the prior art relied on is part of the common general knowledge, as noted above (*Valeant* at para 48, citing *Eli Lilly and General Tire*) and explained below.

[612] The parties disagree on the state of the art. Pharmascience cites several studies and abstracts that it argues provide the mosaic of art to support that the claimed subject matter of the '802 Patent was obvious. Teva argues that much of this prior art was not well known, included brief abstracts that reported on pilot or Phase II studies, would not turn up in a search (and that some did not in fact turn up in Dr. Green's own search), and/or that these references were not part of the common general knowledge. Teva submits that Pharmascience and its expert, Dr. Green, have cobbled together abstracts, lesser known articles, and patent applications in hindsight to create a mosaic of art to argue that the POSITA would arrive at the invention with ease. Teva submits that there is no justification for a POSITA to piece together this mosaic.

[613] The expert's opinions on how the prior art cited would or would not guide the POSITA is addressed in the discussion on obviousness.

[614] The key prior art that is relied on by Pharmascience is set out below.

A. *Prior art on glatiramer acetate 20 mg daily vs. every-other-day (alternate-day)*

[615] Flechter et al, "Copolymer 1 (Glatiramer acetate) in relapsing forms of multiple sclerosis: Open multicenter study of alternate-day administration", 2002 Clin Neuropharm 25(1): 11-15 [Flechter 2002] is an open-label pilot study that compared the efficacy of glatiramer acetate 20 mg administered daily and on alternate days (i.e., every-other-day). In the study, 68 patients with relapsing forms of MS received glatiramer acetate 20 mg every other day. The author then compared the results of this study with the results of a previous study (i.e., Meiner 1997) that had studied the efficacy of glatiramer acetate 20 mg administered daily. Based on the comparison, the authors concluded that the results of this trial suggest that every-other-day treatment is "safe, well-tolerated and probably as effective as daily [treatment] in reducing relapse rate and slowing neurologic deterioration" in patients.

[616] Fletcher et al, "Comparison of glatiramer acetate (Copaxone®) and interferon β-1b (Betaferon®) in multiple sclerosis patients: an open-label 2-year follow-up" 2002 J Neurological Sci 197: 51-55, reported the results of a 2-year open-label follow-up study in the efficacy and safety of glatiramer acetate 20 mg daily, glatiramer acetate 20 mg alternate-day, and Betaseron 8 MIU alternate-day administered to patients with relapsing forms of MS. Each treatment arm had no more than 20 patients. The authors reported that the three treatment options showed equal efficacy for the control of MS exacerbations and similar adverse event profiles.

[617] As noted above, Rebif is an interferon that was first approved in 2002 by the U.S. Food and Drug Administration [FDA]. Rebif is indicated for treatment of patients with RRMS. According to the 2005 product label and 2006 product monograph of Rebif, this interferon is

administered subcutaneously three times a week as a 22 µg or 44 µg dose. The doses are administered at least 48 hours apart.

[618] Khan et al, "Randomized, prospective, rater-blinded, four-year, pilot study to compare the effect of daily versus every-other-day glatiramer acetate subcutaneous injections in relapsing-remitting multiple sclerosis", 2008 Multiple Sclerosis 14:S296 (P902) [Khan 2008] and Caon et al, "Randomized, prospective, rater-blinded, four year pilot study to compare the effect of daily versus every-other-day glatiramer acetate 20 mg subcutaneous injections in RRMS", 2009 Neurol 72(11)(Suppl 3): A317 [Caon 2009] are both abstracts (less than a page each) from a meeting/conference that described the results of the same 4-year, randomized, prospective, rater-blinded study (i.e., where the assessors are not told which patients are in which group) of patients who were treated with 20 mg glatiramer acetate administered daily or every-other-day.

[619] Thirty RRMS patients were randomized to each treatment group and followed for two years. Thereafter, patients in each group were given the option to continue or switch to the other group and then they were followed for another two years. The authors reported that the study revealed no difference in the relapse rate, disease progression, and change in T2-weighted lesion volume or Gd enhancing lesions between the two groups after two years of study. At the two-year mark, all patients in the daily group opted to switch to the every-other-day dosing regimen. After four years, the authors reported no difference between the two treatment groups. The authors concluded, "[t]his pilot study suggests that GA 20 mg [subcutaneous] administered [daily] or [every-other-day] may be equally effective in RRMS."

B. *Prior art on glatiramer acetate 20 mg vs. 40 mg administered daily*

[620] Rovaris et al, "Results of a randomized, double-blind, parallel-group study assessing safety and efficacy of 40mg vs 20mg of glatiramer acetate on MRI-measured disease activity in relapsing-remitting multiple sclerosis", 2006 J Neurology 253 (Suppl 2): P570 is an abstract (less than a page) that described the results of a 9-month randomized, double-blind, parallel-group study assessing the safety and efficacy of 40 mg vs. 20 mg of glatiramer acetate subcutaneous administered daily. The authors concluded, "[o]ver a nine-month period of observation, GA 40 mg is safe, well-tolerated and more effective than the currently approved 20 mg dose in reducing MRI activity and relapse rate in patients with RRMS."

[621] Cohen 2007, as mentioned above, reported on the results of Teva's FORTE Phase II study, which was a randomized, double-blind, dose comparison study of glatiramer acetate 40 mg vs. 20 mg in patients with RRMS. Ninety patients were randomly assigned to the 20 mg or 40 mg daily regimens. The authors state that the primary efficacy endpoint "showed a trend favoring the 40-mg group". The authors concluded that the 40 mg daily regimen "was safe and well tolerated," and that "[t]he overall efficacy results suggested that a 40-mg dose of [glatiramer acetate] may be more effective than the currently approved 20-mg daily dose in reducing MRI activity and clinical relapses."

[622] Teva's press release, entitled "Data Published in Neurology Showed That Higher Dose of Copaxone® Increased Efficacy in Relapsing-Remitting Multiple Sclerosis (Rms)", dated April

17, 2007 publicized the results of the phase II trial, as published in *Neurology*, and confirmed the initiation of the phase III trial.

[623] Comi et al, "Results from a phase III, one-year, randomized, double-blind, parallel-group, dose-comparison study with glatiramer acetate in relapsing-remitting multiple sclerosis", 2008 Multiple Sclerosis 79(14): S299-301 [Comi 2008 or FORTE Phase III] is an abstract that reported on the results of the Phase III clinical trial, which was done to confirm the results of the phase II study. The study evaluated "the safety, tolerability, and efficacy of GA 40 mg compared to the 20 mg dose" administered daily in patients with RRMS. The study was a 1-year, multi-national, multi-centre, randomized, double-blind, parallel-group study that involved 1,155 patients. The authors reported that both the 40 mg and 20 mg group "showed a reduction in the mean number of gadolinium-enhancing and new T2 lesions over time with a trend for a faster reduction in the first trimester in the 40 mg dose compared with 20 mg dose." It further reported that "[b]oth doses were well-tolerated with a safety profile similar to that observed in previous studies of 20 mg GA." The authors concluded that "[i]n RRMS patients, both GA 40 mg and the currently approved 20 mg doses were safe and well-tolerated, and were equally effective in reducing clinical relapses and MRI activity."

[624] Teva's press release, entitled "Teva Provides Update on FORTE Trial", dated July 7, 2008 stated, "[t]he 40 mg dose did not demonstrate increased efficacy in reducing the relapse rate; however, the higher dose maintained the favorable safety and tolerability profile of COPAXONE® 20 mg."

C. *Prior art on glatiramer acetate 40 mg every-other-day*

[625] As noted above at Part XVI, Pinchasi 2007 is an international patent application that was not approved. The patent application describes "a method of alleviating a symptom of a patient suffering from a relapsing form of multiple sclerosis which comprises periodically administering to the patient by subcutaneous injection a single dose of a pharmaceutical composition comprising 40 mg of glatiramer acetate so as to thereby alleviate the symptom of the patient. . . ." In one embodiment, periodic administration is daily. In another embodiment, the periodic administration is every other day. The patent application, in example 1, discloses the trial data from the FORTE Phase II study (i.e., Cohen 2007 which studied 40 mg vs. 20 mg daily).

[626] Pharmascience appears to suggest that the '437 Patent is prior art to the '802 Patent. However, the' 437 Patent, as construed above, is addressed to CIS patients, not RRMS, and teaches the use of 20 mg glatiramer acetate daily, with one claim of 40 mg. The '437 Patent does not refer to any other dosing regimen except daily.

D. *Prior art on injection site reaction and immediate post injection reaction*

[627] Edgar et al, "Lipoatrophy in patients with multiple sclerosis on glatiramer acetate", 2004 Can J Neurol Sci 31: 58-63 [Edgar 2004], reported the results of a study that examined the relationship between lipoatrophy and patient characteristics in 76 RRMS patients using glatiramer acetate. Over six months, during regular clinic appointments, physicians assessed

these patients' injection site areas through visual inspection and manual palpation. The study reported that 45% had evidence of lipoatrophy in at least one injection site area, which was much higher than expected.

[628] Devonshire et al, "The Global Adherence Project – A multicentre observational study on adherence to disease-modifying therapies in patients suffering from relapsing-remitting multiple sclerosis", 2006 Multiple Sclerosis 12:S1 (P316) [Devonshire 2006], is an abstract published in *Multiple Sclerosis Journal*. The Global Adherence Project is the largest global, observational study that has evaluated real-world adherence rates to approved DMTs for RRMS. This study retrospectively surveyed over 2,600 patients from 22 countries who were on one of the DMTs for at least six months. The study found that 25.3% of patients reported non-adherence and that the non-adherence rate was significantly lower for Avonex (administered once weekly) than for Rebif, Betaferon/Betaseron, and Copaxone (administered daily). The most common reason for non-adherence was forgetting to administer the injection.

XXIII. Overview of the Experts' Evidence on the '802 Patent

A. *Pharmascience's Expert, Dr. Green*

[629] In Dr. Green's opinion, the claims of the '802 Patent were obvious. Dr. Green stated that there were no material differences between the state of the art in August 2009 and the subject matter of the claims.

[630] Dr. Green's opinion is that the state of the art in August 2009 demonstrated at least that: reduced-frequency dosage regimens of DMT were known; a 40 mg daily-dose of glatiramer acetate was at least as safe and efficacious as a 20 mg daily-dose; reduced frequency of injections would reasonably be presumed to result in reduced injection site irritation and reaction; and, that Teva, based on its Pinchasi patent application, believed that the periodic administration of 40 mg glatiramer acetate, including on an every-other-day basis, would be effective to treat MS.

[631] Dr. Green added that the only possible difference would be between an every-other-day dosage regimen of 40 mg of glatiramer acetate (as taught in Pinchasi 2007) and the claimed three times per week dosage regimen of 40 mg of glatiramer acetate (with at least one day between each injection).

[632] Dr. Green opined that the difference could have been easily bridged by the POSITA using their common general knowledge and other information, which could have been located by making a reasonably diligent search and making deductions. Dr. Green added that the POSITA would be motivated to reduce injection frequency to reduce injection site reactions and a three times weekly regimen would also be more convenient.

B. *Teva's Expert, Dr. Prat*

[633] In Dr. Prat's opinion, the claims of the '802 Patent were not obvious; there were differences between the state of the art and the subject matter of the claims and it would have required inventive ingenuity to obtain the invention.

[634] Dr. Prat stated that some of the prior art cited by Dr. Green would not be known by the POSITA or it would not be given much weight and would not be part of the common general knowledge.

[635] With respect to the state of the art in August 2009, Dr. Prat explained that reduced frequency of administration of 40 mg glatiramer acetate was not known by the POSITA. Dr. Prat stated that there was no disclosure in the prior art cited by Dr. Green that glatiramer acetate should be used for treating RRMS and/or CIS at a dose of 40 mg three times a week with at least a day between each injection. There was also no disclosure of the claimed efficacy of such a regimen.

[636] Dr. Prat concluded that there was nothing in the prior art that would point the POSITA towards using 40 mg of glatiramer acetate three-times-a-week given that 40 mg daily was shown to be about as effective as 20 mg daily but that 40 mg daily resulted in increased adverse events and increased patient discontinuation of the therapy. Dr. Prat emphasized that 20 mg glatiramer acetate daily was known to be optimal and a daily dosing regimen was easier to follow.

[637] In Dr. Prat's opinion, the POSITA would not see any reason to increase the dosage to achieve similar efficacy but have increased adverse events.

C. *Teva's Expert, Dr. Day*

[638] Dr. Day provided his opinion as a statistician with expertise in clinical trial design and interpretation, on how the POSITA would regard the prior art relied on by Pharmascience. Dr. Day explained, among other things, the purpose of a well-designed clinical trial and the importance of sample size, randomization, blinding and statistical significance. Dr. Day assessed the prior art cited and noted the features that inform the assessment of the results or the report.

[639] Dr. Day noted that Pinchasi 2007 was a patent application. Dr. Day explained that the example in the application would be of most relevance to the POSITA. The example disclosed trial data from the study comparing 40 mg and 20 mg glatiramer acetate administered daily (i.e., Cohen 2007). Dr. Day noted that Cohen 2007 was a well-designed trial, but the conclusions were overstated. Dr. Day stated that the POSITA would be sceptical of the results that showed a faster onset of action for the 40 mg dose at the three-month mark as this was a secondary endpoint and not statistically significant. Dr. Day also noted that Cohen 2007 engaged only 90 patients, and 12 dropped out. Dr. Day noted that the statistical analysis of efficacy did not account for the drop-outs which would raise a concern about the reliability of the conclusions.

[640] Dr. Day opined that, taking the disclosure of all of the prior art documents together, the POSITA would conclude that 40 mg and 20 mg daily regimens are of similar efficacy, but that the 40 mg dose did <u>not</u> demonstrate increased efficacy in reducing the relapse rate, as noted in Teva's press releases and confirmed in Professor Comi's report (Comi 2008) and presentation slides about the FORTE Phase III trial. Dr. Day added that the POSITA would also note that

there is conflicting evidence regarding the safety or tolerability of the two dosing regimens and that Professor Comi's slide 14 indicated that almost twice as many patients in the 40 mg group withdrew because of adverse events.

[641] Dr. Day also opined that the POSITA would conclude that in 2009 there were no well-designed trials about the relative efficacy of glatiramer acetate 20 mg every other day and 20 mg daily. He noted that a large, randomized, double-blinded, controlled trial would be needed to draw a meaningful conclusion about the relative efficacy, safety and tolerability of the two regimens.

XXIV. Is the '802 Patent Invalid due to Obviousness?

A. *Teva's Submissions*

[642] According to Teva, as of August 2009, the common general knowledge was that daily administration of Copaxone 20 mg was known to treat RRMS and CIS, and that glatiramer acetate had a poorly understood mechanism of action, but that it differed from the interferons. The common general knowledge also included some of the results from reliable clinical studies.

[643] Teva submits that Dr. Green's presentation of the common general knowledge was not balanced and not consistent with the manner in which he addressed common general knowledge before the U.K. Court (as discussed above). Teva submits that Dr. Green attributed almost every

document he cited to the common general knowledge. Dr. Green pointed to abstracts, pilot studies, and short papers in lesser-known journals.

[644] Teva notes that Dr. Green attached a 149-page list of articles and abstracts from PubMed searches. Dr. Green's search revealed over thirteen hundred articles, yet Dr. Green did not explain why he relied on specific pieces of prior art to advocate that the patent is obvious. Moreover, some of the prior art he relied on did not come up in the search he conducted. Teva submits that Dr. Green used a results based and hindsight approach to identify minor abstracts and articles to support Pharmascience's argument and ignored articles that did not. Teva submits that, although a mosaic of art can be relied on, the mosaic must be of the prior art that the POSITA would have been led to combine.

[645] For example, Teva submits that Pinchasi 2007, a patent application, would not be looked for by a POSITA and would only be found in hindsight. Teva notes that Dr. Green did not conduct a patent search himself. Teva adds that the 1996 U.S. Federal Drug Administration Summary Basis of Approval [FDA SBOA] document would not be sought or found, noting that Dr. Green was not even aware of this until years after 2009.

[646] With respect to patient adherence, Dr. Green cited only one abstract (Devonshire 2006) to support his characterization of the common general knowledge. Dr. Green admitted that the skilled person may not have read Devonshire by August 2009 and contained minimal information.

[647] Teva submits that the common general knowledge was that interferons, with reduced frequency administration, did not have better adherence than Copaxone. Teva submits that Dr. Green's report omitted the information in the other articles that did not support his view, although he had located them in his own PubMed search.

[648] With respect to the state of the art, Teva submits that there was no prior art that disclosed the use of 40 mg glatiramer acetate three times a week.

[649] Teva acknowledges that Flechter 2002, Khan 2008 (and Caon 2009, which referred to the same study) suggested that 20 mg could be used every other day; however, these short abstracts reporting on pilot studies would not have guided the POSITA. Teva adds that Dr. Green acknowledged the he was not aware of Flechter 2002 in 2009, but only later in the context of this litigation.

[650] Teva also notes that Dr. Green agreed that he had never advised a patient to use 20 mg every other day.

[651] Teva submits that other authors' references to these studies does not increase their value. Nor does the evidence of Dr. Selchen and Dr. Morrow who acknowledged that they had considered the results of other, unrelated open label studies. Teva notes that there is no evidence that the open label studies referred to by Dr. Selchen or Morrow were as poorly designed as Khan 2008/Caon 2009 or Flechter 2002, how they differed, or how their results were interpreted in relation to their design.

[652] With respect to Pharmascience's reliance on the FDA SBOA for Copaxone in 1996, Teva notes that this document would not be found or read by the POSITA. Moreover, the SBOA did not disclose or suggest any particular dose or schedule, let alone 40 mg three times a week and the reviewer's questioning was based on an incorrect understanding of the drug. Teva also notes that Dr. Green conceded that he was not aware of the SBOA in 2009, rather he only learned of it at some point between 2012 and 2016.

[653] Teva submits that Cohen 2007 reported on 40 mg glatiramer acetate in a Phase II trial. However, the subsequent Phase III trial, reported in Comi 2008, was not considered to be successful as it demonstrated that 40 mg daily did not have better efficacy than 20 mg daily and caused increased adverse reactions from injection site reactions which were "statistically significant compared to GA 20mg".

[654] Teva submits that Pinchasi 2007 was a patent application that the POSITA would not look for or be aware of. Teva notes that Pinchasi 2007 was focussed on daily administration and there was only a bare suggestion to administer 40 mg every other day.

[655] Teva notes that, as of 2009, there were several interferon therapies for RRMS, each with different dosing schedules. For, example, Rebif was administered three times a week. Teva submits that the POSITA would not be guided to consider a three times per week dosing schedule for glatiramer acetate based on the interferons. Teva again notes that the interferons differed in their mechanism of action.

[656] Teva acknowledges that patient adherence to DMTs was an issue, as mentioned in the ‘802 Patent. Teva submits that the prior art demonstrated that the interferons did not have better patient adherence than Copaxone. Rather studies found that Copaxone 20 mg daily had equal or better adherence than the interferons.

[657] Teva submits that the studies did not demonstrate that reducing injection frequency would improve adherence.

[658] Teva argues that there was no reliable art pointing to an every other day administration of any dose of glatiramer acetate. More particularly, Teva submits that no art pointed to three times a week regimen for glatiramer acetate (at any dosage), or suggested that it would have the claimed attributes of the ‘802 Patent. Teva notes that Dr. Green admitted on cross-examination that the prior art did not disclose 40 mg three times per week. Teva adds that there is no evidence to support Dr. Green’s “bald statement” that 40 mg three times a week is therapeutically equivalent to 40 mg every other day.

[659] Teva submits that there were differences between the state of the art and the subject matter of the claims. Teva adds that these differences existed even if Dr. Green’s mosaic of art were relied on.

[660] Teva further submits that the differences would not be obvious to the POSITA; inventiveness was required.

[661] Teva submits that Pharmascience has not met its burden of demonstrating that relevant prior art existed or that the POSITA in 2009, even if they located the prior art, would have combined the prior art to reach the subject matter of the claims (*Laboratoires Servier, Adir, Oril Industries, Servier Canada Inc v Apotex Inc*, 2008 FC 825 at para 254 [*Servier*]; *Biovail Corporation v Canada (Health)*, 2010 FC 46 at para 84; *Camso Inc v Soucy International Inc*, 2019 FC 255 at para 125).

[662] Teva submits that it is only in hindsight that that the POSITA would use 40 mg glatiramer acetate three times per week. Teva points to *Free World Trust v Électro Santé Inc*, 2000 SCC 66 at para 25, where the Supreme Court noted that, "it is all too easy after an invention has been disclosed to find its antecedents in bits and pieces of earlier learning. It takes little ingenuity to assemble a dossier of prior art with the benefit of 20-20 hindsight."

[663] Teva points out that some of the references Dr. Green cited were not part of his PubMed searches, including Pinchasi 2007, Khan 2008, Caon 2009, Devonshire 2006, and the FDA SBOA. Teva adds that Dr. Green did not explain why the POSITA would find or combine the cited references without having first reviewed the patent.

[664] Teva argues that the POSITA would not look for or review patent applications, such as Pinchasi 2007. Teva further argues that the POSITA would not piece together the FDA SBOA or Pinchasi 2007, even if they found these, with the other art relied on by Pharmascience.

[665] Teva submits that, although Dr. Khan was well regarded, the Khan 2008 abstract was little known. Caon 2009 is also a short abstract reporting on the same study as Khan 2008. Teva reiterates that the POSITA would not give these short abstracts any weight.

[666] Teva notes that Pharmascience directed Drs. Prat and Day to the GALA study protocol's reference to Khan 2008 and Flechter 2002. However, Pharmascience disregarded the subsequent statement in the protocol which confirmed that the "studies were clearly too small and underpowered to show a significant effect on clinical end-points".

[667] Teva disputes Dr. Green's opinion that 40 mg three times weekly fell within the weekly dose ranges previously disclosed. Teva notes that Dr. Green acknowledged that it was not known whether the same total weekly dose would be effective when administered differently.

[668] Teva adds that Dr. Green's basis for the obviousness of three times weekly dosing is that Rebif, an interferon, was administered three times weekly. Teva points to Dr. Prat, who stated that the POSITA would "never consider that a specific dosing regimen of Rebif would equally work for Copaxone". Teva notes that the experts agreed that the interferons have different mechanisms of action, different side effects and different pharmacokinetics. Teva adds that all the interferons are administered at substantially different doses and frequency.

[669] Teva notes that its invention changed both the dose (20 to 40 mg) and the regimen (daily to three times weekly). Teva submits that the POSITA "having no scintilla of inventiveness or

imagination" would not have "come directly and without difficulty to the solution taught by the patent".

[670] Teva notes that whether a piece of prior art would have been located by the skilled person is relevant to the obvious to try step of the *Sanofi* test, including that the skilled person "might not have thought to combine that prior art reference with other prior art to make the claimed invention" (*Hospira* at para 86).

[671] Teva disputes that it was self-evident that 40 mg three times weekly would improve adherence and compliance, as Dr. Green contended. Teva notes that many factors influence adherence, as all the experts acknowledged.

[672] With respect to the effort required to achieve the invention, Teva disputes Dr. Green's evidence that it would be the normal or routine role of a clinician to discuss options with patients and to advise them to self-administer 40 mg glatiramer acetate three times per week. Teva notes Dr. Green's inconsistent evidence regarding off-label use.

[673] Teva adds that there was no motivation to try 40 mg three times a week. As conceded by Dr. Green, no prior art directed the skilled person to do so.

[674] Teva disputes that the side effects of frequent injection would motivate the POSITA to look for less frequent injections. Dr. Green relied only on his view of common sense. However,

the prior art (found in Dr. Green's literature search but omitted from his report) disclosed that interferon therapies with reduced frequency administration did not result in improved adherence.

[675] Teva adds that if there was motivation to address the effects of injection, the POSITA would look to non-injectable therapies.

[676] Teva explains that its actual course of conduct was not routine or straightforward. Teva notes that there were several unsuccessful trials in its effort to improve Copaxone before pursuing 40 mg three times per week.

[677] Teva disputes Pharmascience's suggestion that this Court should be influenced by other proceedings regarding the '802 Patent or equivalent patents. Teva notes that decisions of foreign courts are not to be considered (*Eli Lilly Canada Inc v Mylan Pharmaceuticals ULC*, 2015 FC 17 at para 66 [*Mylan*], citing *Eli Lilly Canada Inc v Apotex Inc*, 2007 FC 455 at para 244, aff'd 2008 FCA 44). Teva notes that there are differences in practice and procedure and differences in the evidence presented.

B. *Pharmascience's Submissions*

[678] Pharmascience submits that the '802 Patent is obvious; there were no material differences between the state of the art and the subject matter of the claims and any minor differences would easily be bridged by the POSITA.

[679] Pharmascience submits that the state of the art as of August 2009 was that:

- reduced frequency of injections was associated with reduced injection-site irritation and reaction and better tolerance (which led to improved patient compliance and adherence);

- Flechter 2002, Khan 2008 and Caon 2009 described the safety and effectiveness of every-other-day administration of 20 mg glatiramer acetate;

- Cohen 2007 and Comi 2008 described the safety and effectiveness of 40 mg glatiramer acetate;

- Rebif, an interferon, used to treat patients with RRMS was administered three times per week (and with a day in between injections);

- all of the interferons (Avonex, Rebif and Betaseron) were administered less frequently than daily; and,

- Pinchasi 2007 described and claimed the use of 40 mg glatiramer acetate every-other-day for the treatment of patients with RRMS.

[680] Pharmascience argues that moving from the state of the art, which in its view, taught the every-other-day dosing regimen of 40 mg glatiramer acetate, to a fixed three times per week

dosing regimen of 40 mg glatiramer acetate (which only results in one less dose in a two week period) would have been obvious to the POSITA to improve patient convenience and adherence. Pharmascience suggests that fixed day dosing is easier to remember and that less frequent injections would reduce injection site reactions and post injection reactions.

[681] Pharmascience submits that as of August 2009 it was known that daily administration of glatiramer acetate by injection commonly caused injection site reactions including, erythema (redness), pain, mass pruritus (itching), edema, inflammation and hypersensitivity.

[682] Pharmascience focuses on lipoatrophy, a side effect of frequent injection, and submits that it has irreversible impact. Pharmascience submits that the lipoatrophy that occurred as a result of daily Copaxone injections was permanent, disfiguring and relatively common.

[683] Pharmascience argues that common sense dictated that reducing the frequency of injections also reduced injection site reactions and led to better tolerance and, in turn, improved patient compliance and adherence. Pharmascience submits that some studies support this assumption.

[684] Pharmascience points to Flechter 2002, Khan 2008 and Caon 2009 in support of its submissions that every other day dosing of 20 mg glatiramer acetate was as effective as daily administration. Pharmascience also points to a single line in Caon 2009 that injection site lipoatrophy was significantly less in the every other day group of patients.

[685] Pharmascience submits that, as of August 2009, 40 mg glatiramer acetate was a known, effective and safe dose for the treatment of patients with RRMS. Pharmascience points to Teva's Phase II and Phase III clinical trials (Cohen 2007 and Comi 2008), which compared daily injection of 40 mg Copaxone and 20 mg Copaxone in RRMS patients. Pharmascience notes that the studies found both doses to be well tolerated and equally effective in reducing clinical relapses and MRI activity. Pharmascience also emphasizes that the studies found that the 40 mg dose demonstrated a trend for faster results in the first few months with respect to the number of lesions.

[686] Pharmascience submits that Pinchasi 2007 claimed 40 mg of glatiramer acetate, injected periodically, including every-other-day, for the treatment of patients with RRMS.

[687] Pharmascience also relies on the interferon DMTs, in particular, Rebif, which was injected three times per week. The other interferons Avonex and Betaseron had different regimens but all were administered less frequently than daily. Pharmascience submits that, among the interferons, the less frequent dosing regimens encouraged patient adherence and compliance relative to the most-frequently administered product.

[688] Pharmascience alleges that Teva has taken a "scorched-earth" approach to the state of the art by arguing that none or little of it taught anything. Pharmascience disputes Teva's suggestion that its own Comi 2008 clinical trial was a "failure" that would lead a POSITA to think that there was no 40 mg product under development. Pharmascience disputes that the POSITA would be unaware of Flechter 2002, Khan 2008 and Caon 2009 or would ignore these studies because they

were not Phase III clinical trials. Pharmascience also disputes that Pinchasi 2007 would not be found or would be ignored because it did not disclose any clinical studies on a 40 mg dose administered every-other-day and because it never issued as a patent. Pharmascience further disputes that the Rebif three times a week regimen would be entirely ignored by the skilled person because the mechanisms of action of interferon and glatiramer acetate were understood to be different.

[689] Pharmascience adds that Teva's conduct was inconsistent with its current approach. For example, Teva's 2008 press release regarding the FORTE Phase III study did not cast it as a failure rather that "the higher dose maintained the favourable safety and tolerability profile of Copaxone 20 mg".

[690] Pharmascience submits that there are no material differences between the state of the art and the subject matter of the claims. The only minor difference would be the use of 40 mg of glatiramer acetate, by injection periodically, including "every-other-day" (Pinchasi 2007) and the use of 40 mg of glatiramer acetate, by injection three times per week, with a day between injections.

[691] Pharmascience submits that the common general knowledge, common sense and motivation to address injection site reactions would lead to the invention. It was self-evident that reducing the frequency of injections would improve tolerability and reduce injection site reactions and irritation, without compromising efficacy.

[692] Pharmascience argues that moving to a three times weekly regimen on fixed days would have been obvious to improve patient convenience as it is easier to remember and would avoid weekend injections. Pharmascience submits that Teva's expert, Dr. Prat, agreed that three times a week is an improvement over Pinchasi 2007's every other day regimen. Pharmascience adds that Rebif provided an example as it was administered three times weekly.

[693] Pharmascience is critical of Dr. Prat's suggestion that the POSITA would not be motivated to develop a 40 mg dose but would instead look to an oral formulation. Pharmascience notes that the oral formulation had been a failure.

[694] Pharmascience again submits that the Court should draw an adverse inference from the lack of evidence from the inventors, who could have explained the course of conduct in the invention.

[695] Pharmascience submits that the evidence of Teva's expert, Dr. Kreitman, was unrelated to the work leading to the '802 Patent. Dr. Kreitman stated that only a few meetings were held to discuss a higher-dose, lower-frequency regimen for glatiramer acetate – one in November 2008 and one in June 2009, resulting in a decision to proceed with a Phase III clinical trial (i.e., the eventual GALA trial).

[696] Pharmascience submits that Dr. Kreitman acknowledged that Teva's work was aimed at pursuing the 40 mg product because the patent for Teva's 20 mg glatiramer acetate was soon

expiring and Teva was concerned that the generic version of 20 mg glatiramer acetate would be used three times per week rather than the 40 mg product.

[697] Pharmascience also notes that Dr. Kreitman indicated that 40 mg three times per week was among the first few higher-dose, lower-frequency dosing regimens that were considered by Teva.

[698] Pharmascience suggests that the Court should infer that the GALA trial was undertaken only to confirm what was obvious, i.e., that 40 mg three times per week would be just as safe and effective as 20 mg daily, and would improve tolerability (e.g., fewer injection site reactions).

[699] Pharmascience argues that the evidence of Dr. Green should be relied on over that of Teva's experts. Pharmascience characterizes Drs. Day and Prat as sceptics and less qualified to opine on the key issues than Dr. Green. Pharmascience suggests that Dr. Day's evidence be ignored completely because his perspective as a biostatistician is not relevant and he has a history of criticising even highly reputable scientists.

[700] Pharmascience further argues that the Court should consider that patents equivalent to the '802 Patent have been found to be obvious, including in the U.K. and U.S. In addition, Pharmascience notes that the CIPO is currently re-examining the '802 Patent.

C. *What do the Experts Say?*

(1) Dr. Green

[701] In Dr. Green's opinion, the claims of the '802 Patent were obvious. Dr. Green stated that there were no differences between the state of the art in August 2009 and the subject matter of the claims.

[702] Dr. Green stated that, by August 2009, it was recognized that the 20 mg daily dose had been arbitrarily selected as there had been no determinative study to establish the ideal dosage regimen for glatiramer acetate. Dr. Green noted that less frequent dosing regimens of 20 mg glatiramer acetate were also known and continued to be investigated. Dr. Green referred to Khan 2008, who built on the work of Flechter 2002.

[703] Dr. Green stated that the POSITA would know that other doses of glatiramer acetate were being explored, including a 40 mg dose, based on the FORTE Phase II Study reported by Cohen in 2007.

[704] Dr. Green added that the results of FORTE Phase III clinical trials were widely reported, including by way of Teva's July 2008 press release. Dr. Green noted that Comi 2008 reported on the results of this Phase III clinical study and concluded that both the 40 mg and 20 mg doses were safe and well tolerated in RRMS patients and equally effective in reducing clinical relapses and MRI activity. Dr. Green noted that the abstract stated that both doses showed a reduction in Gd-enhancing and new T2 lesions over time, but noted a trend for faster reduction in the first three months with the 40 mg dose.

[705] In Dr. Green's opinion, the combination of this knowledge was that the 20 mg dose was not the necessary dose to achieve clinical efficacy; it could be achieved with alternate dosages and dosing regimens.

[706] Dr. Green explained that because MS is a chronic condition, compliance and adherence to long-term treatment is a concern. (Dr. Green explained that compliance refers to the degree to which a patient takes the medication as prescribed. Adherence refers to the degree to which a patient follows the physician's instructions more broadly. He added that the terms are often used interchangeably).

[707] Dr. Green stated that unpleasant side effects of injection were known to lead to issues with patient compliance. Dr. Green opined that it would be common sense to the POSITA that less frequent injections would result in increased compliance. Dr. Green cited the Global Adherence Project (Devonshire 2006) in support of his view. He noted that, although there may be other contributing factors, the prevailing trend was that increased injection was associated with reduced compliance or adherence.

[708] Dr. Green also noted that the Johnson study (1995) found that 90% of patients taking glatiramer acetate experienced injection site reactions. Dr. Green noted that injection site reactions include pain, discomfort, skin change, "even lipoatrophy", all of which are unpleasant but not frightening.

[709] Dr. Green noted that Pinchasi 2007 relied on the Cohen 2007 Phase II study results in stating that the 20 mg and 40 mg daily had been shown to reduce MRI measured enhancing lesions in MS patients. Dr. Green stated that, if 20 mg is efficacious for this purpose, then a POSITA would expect that 40 mg would also work as a treatment for patients at risk of developing MS.

[710] Dr. Green stated in his report and in his oral evidence that there were three key messages for the POSITA in Pinchasi 2007:

- 40 mg daily glatiramer acetate significantly improved efficacy without an increase in adverse reactions. Dr. Green is of the view that the POSITA would have this view because they would read Pinchasi 2007 with the knowledge of Cohen 2007 and Comi 2008 and would have identified that there was good safety and tolerability for the 40 mg glatiramer acetate. This would have reinforced that the FORTE trials were to be believed – i.e., that there is an enhanced onset of action; that there was a suggestion that 40 mg could be given every other day and would be equally or more efficacious.

- Pinchasi 2007 reported on the faster onset of action of the 40 mg dose compared to the 20 mg (based on Cohen 2007 and Professor Comi's presentation of the FORTE Phase III trial).

- The POSITA would be interested in Pinchasi 2007's periodic administration and would read this with the knowledge of Khan 2008.

[711] Dr. Green's opinion is that the state of the art in August 2009 taught that:

- Reduced-frequency dosage regimens of DMTs, including 20 mg glatiramer acetate, were known to be as effective in treating MS but better-tolerated than daily-dosage regimens, leading to improved patient compliance and adherence;
- A 40 mg daily-dose of glatiramer acetate was at least as safe and efficacious as a 20 mg daily-dose and was well-tolerated by patients, with potentially an earlier onset of action and increased effectiveness in reducing MRI activity and clinical relapses;
- Reduced frequency of injections would reasonably be presumed to result in reduced injection site irritation and reaction, especially for a medicine where the injection site could remain inflamed or irritated in the period after injection; and,
- Teva believed that the periodic administration of 40 mg glatiramer acetate, including on an every-other-day basis, would be effective to treat MS (based on Pinchasi 2007).

[712] On cross-examination, Dr. Green acknowledged that his PubMed search regarding the '802 Patent, did not turn up the FDA SBOA document, Khan 2008, Caon 2009 or Devonshire 2006. Dr. Green acknowledged that in 2009, the POSITA would not likely have read Devonshire 2006.

[713] Dr. Green also acknowledged that in 2009, he was not aware of the 1996 FDA SBOA or the questioning posed to the applicant. Dr. Green also acknowledged that in his deposition in

California in 2016, he stated that he became aware of the FDA SBOA sometime between 2012 and 2016.

[714] Dr. Green acknowledged that he was not aware of Flechter 2002 in 2009, but had attached it to his report.

[715] Dr. Green further acknowledged that Pinchasi 2007 did not turn up in his search, but, on re-examination, he was directed to a footnote in his report, which suggests that Pinchasi 2007 was part of the search he oversaw.

[716] With respect to Khan 2008, which Dr. Green stated taught that reducing frequency of administration from daily to every other day can increase tolerability and compliance while maintaining efficacy, Dr. Green acknowledged that he chose not to change his clinical practice based on Khan 2008. He stated that prior to 2014 he did not advise a patient to take 20 mg glatiramer acetate every other day.

[717] On cross-examination, Dr. Green agreed that there was no piece of prior art referred to in the ‘802 Patent that teaches the administration of glatiramer acetate three times per week. Dr. Green reiterated that, in his view, this was the common sense approach.

[718] Based on his view of the state of the art, Dr. Green’s opinion remained that there were no material differences between the state of the art and the subject matter of the claims of the ’802 Patent.

[719] Dr. Green added that the only possible difference would be between an every-other-day dosage regimen of 40 mg of glatiramer acetate (as taught in Pinchasi 2007) and the claimed three times per week dosage regimen of 40 mg of glatiramer acetate (with at least one day between each injection). Dr. Green acknowledged that the three times per week regimen had not been exemplified in the prior art. Dr. Green stated that the dosage difference over 14 days would be small and therapeutically equivalent.

[720] In Dr. Green's opinion, this small difference could be bridged by the POSITA using their common general knowledge and other information available from a reasonably diligent search and making simple deductions.

[721] Dr. Green noted that the tolerability and compliance issues with daily injections would have motivated the POSITA to seek a less frequent administration regimen.

[722] Dr. Green added that the POSITA would have known that three times a week dosing regimens existed for Rebif and that it was more convenient to use a three times a week "formulation" – i.e., the same days every week and that the dose difference over a week would be minor. Dr. Green opined that it would also be well known that three times weekly on the same days of the week would be more convenient and easier to remember.

[723] With respect to Dr. Green's reliance on Devonshire 2006 on patient adherence, Dr. Green agreed that Avonex, which had the best adherence rate (85%) was administered once a week. Copaxone, which had the lowest rate (56.8%), was administered daily.

[724] With respect to Dr. Green's view that it was common sense that reduced injections would increase compliance and adherence and would be self-evident to do so, on cross-examination, Dr. Green acknowledged that Khan 2008 did not recommend a three times weekly dosage although Rebif, previously approved in 2002, had such a dosing schedule.

[725] Dr. Green also acknowledged that Pinchasi 2007, which relied on Cohen 2007 (FORTE Phase II trial), noted that there was a 50% increase in the number of patients who had a potential post injection reaction when given 40 mg. Dr. Green added that the type of reaction was important and that the reactions that occurred with the 20 mg treatment were more concerning.

[726] Dr. Green stated that it would have been self-evident that the 40 mg three times weekly dosing regimen would likely work to effectively treat MS and CIS patients, with increased adherence and compliance, relative to a 20 mg daily dosing regimen. He added that advising MS and CIS patients to self-administer 40 mg glatiramer acetate three times per week rather than every-other-day would be a matter of simply discussing the available options for a dosing schedule with patients, which is the normal, routine work of a clinician.

[727] On cross-examination, Dr. Green clarified that, although he was referring to the administration of a 40 mg dosage as routine, only 20 mg was available in 2009. Dr. Green agreed that, in 2009, a patient would have to inject two doses of 20 mg (two syringes). Dr. Green speculated that the patient could transfer the dosage to another syringe to reduce the number of injections, but appeared to agree that a patient would not be expected to do this.

[728] Dr. Green also agreed that, to evaluate whether 40 mg three times weekly would work, a clinical study would be required. Counsel for Teva asked why it would be routine work to administer 40 mg glatiramer acetate outside of a clinical study. Dr. Green responded that it would "make sense" to posit the use of a three times per week schedule.

[729] Dr. Green acknowledged that in his report in the U.K. litigation, he had stated that the POSITA would seek to conduct a Phase III clinical study with the 40 mg dose. Dr. Green explained that his previous statement was made based on the assumption that the POSITA would be motivated to investigate. Counsel for Teva noted that Dr. Green did not add this qualification to his evidence regarding the '802 Patent. Dr. Green explained that while it would be routine work to discuss and recommend a three times a week dosing schedule, it would not be routine clinical work. To investigate it, a clinical study would be required. Dr. Green agreed that this clarification was not in his report.

(2) Dr. Prat

[730] Dr. Prat did not fully agree with Dr. Green regarding the common general knowledge or the state of the art in 2009. Dr. Prat noted that not all prior art is common general knowledge. Dr. Prat stated that he understood that common general knowledge refers to widely accepted facts.

[731] With respect to clinical trials, Dr. Prat explained (as did Dr. Selchen and Dr. Day) the differences between investigatory or pilot studies and Phase I, II and III trials.

[732] With respect to available therapies for MS in August 2009, Dr. Prat generally agreed with Dr. Green. However, Dr. Prat stated that it was not common general knowledge that a 40 mg dose of glatiramer acetate was under development. Dr. Prat explained that the results of Comi 2008 indicated that the 40 mg dose did not show increased efficacy.

[733] Dr. Prat agreed that Cohen 2007, an abstract on a Phase II clinical trial that compared 20 mg and 40 mg daily administration, showed a faster onset of action for the 40 mg dosage at the three-month point, but explained that this was an exploratory endpoint and was not statistically significant and that after 8-9 months, the results were the same.

[734] Dr. Prat also explained that Cohen 2007 noted that although the same number of patients withdrew in both groups, more patients in the 40 mg group withdrew because of adverse events. Dr. Prat noted that despite conclusions stated by Cohen 2007, the data does not suggest that 40 mg had less adverse reactions.

[735] Dr. Prat acknowledged that the results of Cohen 2007 did not point Teva away from pursuing the Phase III study. However, Dr. Prat explained that the POSITA would not place much, if any, weight on the Phase II results given that the results of the more robust FORTE Phase III study, which investigated 20 mg daily compared to 40 mg daily, were available.

[736] Dr. Prat noted that the subsequent Phase III study and Teva's press releases indicated that "the 40mg dose did not demonstrate increased efficacy in reducing the relapse rate…" and that "the study reaffirms that COPAXONE 20mg… remains the optimal treatment dose…". Dr. Prat

noted that the FORTE Phase III trial reported that 40 mg daily seemed to have increased side effects compared to 20 mg daily that were “statistically significant” and also reported “increased treatment discontinuation due to injection site reactions with the higher [40mg] dose”. Dr. Prat added that, at that time, the POSITA would assume that the 40 mg Copaxone was no longer in development.

[737] Dr. Prat acknowledged that the Phase III trial results were presented by Professor Comi at the World Congress on Treatment and Research in Multiple Sclerosis [World Congress] in 2008. Dr. Prat noted that over 1,200 abstracts were presented. He noted that not every POSITA would have attended Professor Comi’s presentation.

[738] Dr. Prat added that if Comi 2008 were part of the common general knowledge, it would not support using 40 mg of Copaxone.

[739] Dr. Prat disagreed with Dr. Green that the results of the FORTE Phase II and Phase III studies would be part of the common general knowledge, although they were prior art. Dr. Prat stated that although these results were public, they did not form part of the common general knowledge. Dr. Prat noted that not every widely reported clinical study becomes common general knowledge.

[740] Dr. Prat did not share Dr. Green’s view that the 20 mg dose of glatiramer acetate was arbitrarily selected, but he acknowledged that there had not been any dosing studies at the time 20 mg was approved. In Dr. Prat’s view, the results of FORTE Phase III would not lead the

POSITA to consider doubling the dose (20 mg to 40 mg daily) and the lack of a dosing study early in the drug development would not change this.

[741] Dr. Prat stated that although Khan 2008 was available in 2009, it was not part of the common general knowledge. Dr. Prat explained that it was improbable that the POSITA would have seen this abstract or the related presentation, given that it was presented along with approximately 83 oral presentations and at least 900 other abstracts during a 3-day meeting hosting approximately 5,500 participants. He added that this abstract did not disclose well-known principles and would not have been widely accepted.

[742] Dr. Prat added that, if the POSITA had reviewed Khan 2008, they would have given it little, if any, weight because the short abstract described a small, pilot study involving only 30 patients. The study compared 20 mg daily against 20 mg every-other-day glatiramer acetate. Dr. Prat explained that the results of such an insignificant study would not constitute common general knowledge.

[743] With respect to compliance and adherence rates, Dr. Prat explained that the POSITA would understand that adherence is complex and based on multiple factors. Dr. Prat referred to different studies than Dr. Green.

[744] Dr. Prat explained that the pain of injections is not the sole contributor to non-compliance. He noted that it is most often due to forgetting to take the medication. Dr. Prat added that injections of glatiramer acetate are not as painful as for interferons.

[745] Dr. Prat noted that Devonshire 2006 on the Global Adherence Project was a retrospective study. Dr. Prat noted the abstract described a higher non-adherence rate for the higher dose of Rebif as compared to its lower dose. In Dr. Prat's view, if a POSITA considered Rebif at all, this information would point away from a higher dose. Dr. Prat stated that the Devonshire abstract does not even suggest that frequency of administration is a possible cause of non-adherence. Dr. Prat noted that Dr. Green relied on common sense to move to less frequent injections to improve adherence, but this is contradicted by the prior art. Dr. Prat noted that Devonshire 2006 found that forgetting was the main cause.

[746] Dr. Prat noted the article Treadaway, K, "Factors that influence adherence with disease-modifying therapy in MS", 2009 J Neurol 256: 568-576 [Treadaway 2009], which pointed out the problem with comparing data across different dosing regimens, given that some DMTs are administered daily and others weekly. Treadaway 2009 compared adherence rates for Copaxone 20 mg (daily injection) and three interferons: Avonex (once weekly), Betaseron (twice weekly), Rebif (three times weekly). Dr. Prat noted that the authors acknowledged that it was "highly problematic" to compare adherence rates across such varied therapies and attempted to adjust for the variations. Treadaway 2009 reported that Copaxone (daily injection) had slightly better adherence than Avonex (once weekly injection) and had similar adherence to Rebif (three injections per week). Dr. Prat added that Treadaway 2009 surveyed the patients to understand what led to non-adherence and the highest cause indicated was forgetting to take the medication.

[747] With respect to the state of the art, Dr. Prat agreed that, in August 2009, glatiramer acetate 20 mg daily was a known effective treatment for RRMS and CIS. Doctors had been

prescribing Copaxone 20 mg for at least 10 years for RRMS. Copaxone 20 mg had been recently approved for CIS. He also agreed that the 40 mg dose of glatiramer acetate was at least as effective as the 20 mg dose.

[748] Dr. Prat expressed the view that Dr. Green overstated the state of the art regarding the efficacy of 40 mg daily. Dr. Prat noted that Cohen 2007 concluded that there is a suggestion that 40 mg may be more effective than 20 mg daily, but this was not supported by the results of the study. Dr. Prat explained that after nine months, the 40 mg was not more effective. Dr. Prat stated that given that there was no higher efficacy of the 40 mg dose, the potential for post injection reactions and injection site reactions would point away from the 40 mg dose.

[749] Dr. Prat stated that neither he nor other doctors would have been aware of Pinchasi 2007 or patent applications more generally. Dr. Prat added that, even if a doctor were aware of and read Pinchasi 2007, they would understand that its focus was the use of 40 mg of glatiramer acetate *daily.*

[750] Dr. Prat stated that the POSITA would not view Pinchasi 2007 as providing any rational basis for an every-other-day dosing regimen and, in the absence of any data to support 40 mg every other day, the POSITA would give almost no weight to the mention of such a regimen.

[751] In considering whether the ‘802 Patent differed from the state of the art, Dr. Prat noted that in 2009 there was no disclosure in the prior art that glatiramer acetate should be used to treat

RRMS or CIS at a dose of 40 mg either periodically or three times per week with at least a day between.

[752] Dr. Prat disagreed with Dr. Green that it was known that three times per week and every other day doses were therapeutically equivalent.

[753] With respect to reduced frequency dosing, Dr. Prat stated that, to his knowledge, there was no publicly available information showing that a reduced-frequency dosing regimen of glatiramer acetate promoted compliance and adherence.

[754] Dr. Prat noted that the FDA SBOA for Copaxone would not be the type of document a doctor treating MS patients would find or review. Moreover, the author does not identify a dosing schedule and misstates the nature of glatiramer acetate. In Dr. Prat's view, the POSITA would not give any weight to this document, if it were available to them.

[755] Dr. Prat explained that Flechter 2002 reported on an investigatory study. Dr. Prat expressed the view that the suggestion in Flechter 2002 – that 20 mg glatiramer acetate every-other-day is as effective as glatiramer acetate daily – was not supported by sufficient data. Dr. Prat noted that there was no control group and patients self-reported. Dr. Prat also noted that Flechter 2002 stated that, "these preliminary observations will have to be examined in larger studies." Dr. Prat stated that even if the POSITA were to consider Flechter 2002, it would not be clear that alternate day injections represented an improvement over daily injections.

[756] Dr. Prat also noted concerns about Flechter 2002 because it compared 20 mg daily to 20 mg every other day and then compared those results to the results obtained by Meiner in 1997. Dr. Prat noted concerns about cross-study comparisons and pointed out the need to adjust for variabilities between the two cohorts.

[757] On cross-examination, Counsel for Teva posited that the data in Flechter 2002 included an error regarding the relapse rate over two years for 20 mg administered every other day. Counsel for Pharmascience recalculated the relapse rates recorded in Flechter 2002 to attempt to demonstrate that the relapse rate noted was a mistake and that after two years, was highly similar between the two groups and as set out in both Flechter 2002 and Meiner. Dr. Prat acknowledged that, if there were errors in the data and if Counsel's calculation were correct, it showed similar efficacy in relapse rates.

[758] Dr. Prat disagreed with Dr. Green that the Rebif label supports reduced frequency to improve compliance. Dr. Prat again noted that interferons differ from glatiramer acetate and the POSITA would not consider that a specific dosing regimen for Rebif would work equally for Copaxone. He explained that Rebif's efficacy is related to the amount and the frequency of dosing and this does not necessarily apply to Copaxone.

[759] Dr. Prat reiterated that the POSITA would not look at other DMTs, such as Rebif, to arrive at the dosing regimen for glatiramer acetate. Dr. Prat noted several differences between Rebif and glatiramer acetate.

[760] Dr. Prat noted that the mechanism of action of glatiramer acetate is complex and not fully understood but differs from that of interferons. Among other things, Dr. Prat noted that the POSITA understood that frequent administration was likely important for the efficacy of glatiramer acetate because glatiramer acetate degrades quickly after injection.

[761] Dr. Prat also noted that the other interferons had different and unique dosing regimens; Avonex was once per week, Betaseron, every other day and, Rebif, three times per week. There was no reason to select Rebif's dosing regimen for glatiramer acetate.

[762] Dr. Prat agreed that patient adherence was an issue for all DMTs regardless of dosing schedule. Dr. Prat disagreed that one third of missed injections were due to the pain or side effects of the injection. Dr. Prat reiterated that the most common reason cited in the literature was forgetting to take the medication. In Dr. Prat's opinion, it is easier to remember a daily dosing regimen, as it becomes routine at the same time every day.

[763] On cross-examination, Dr. Prat acknowledged that the '802 Patent states that a drawback to glatiramer acetate therapy is the requirement of daily injections, which can be inconvenient. Dr. Prat also acknowledged that the 2009 Copaxone Product Monograph stated that commonly observed adverse reactions were redness, pain, inflammation, itching or a lump at the injection site.

[764] Dr. Prat agreed that fear, avoidance and anxiety were common reactions of some patients regarding injections, but noted that this was usually only at the outset of treatment and did not last.

[765] Dr. Prat also noted that if adverse reactions caused adherence issues, the POSITA would not want to use a higher dose that had been shown to increase those adverse reactions.

[766] With respect to bridging the differences between the state of the art and the subject matter of the claims, Dr. Prat stated that inventiveness would be required. Nothing in the prior art pointed to 40 mg three times per week, FORTE Phase III did not demonstrate any benefit to the higher dose. In Dr. Prat's view, a POSITA would instead be interested in a lower daily dose.

[767] Dr. Prat noted that, even if the POSITA knew that 20 mg every-other-day was effective based on the preliminary studies, such as Khan 2008 (which Dr. Prat noted was underpowered and would not be known or guide), there was no prior art suggesting equivalence between 20 mg every-other-day and 40 mg every-other-day, let alone 40 mg three-times-per-week.

[768] Dr. Prat disagreed with Dr. Green that the invention was obvious to try. In Dr. Prat's opinion, based on the state of the art and the common general knowledge, it would not be self-evident to the POSITA to try a 40 mg three times weekly dosing regimen or self-evident that it would "likely" work to effectively treat MS and CIS patients, with increased adherence and compliance relative to a 20 mg daily dosing regimen.

[769] Dr. Prat explained his disagreement, noting, among other things, that adherence and compliance depend on many factors. He also noted that the prior art taught that reduced frequency would likely result in worse adherence and compliance. Dr. Prat repeatedly stated that daily injections are more easily remembered.

[770] Counsel for Pharmascience suggested that Dr. Prat was not instructed that, in addition to the common general knowledge, the skilled person could consider prior art or information generated by a reasonably diligent search. Dr. Prat responded that a reasonably diligent search would not have turned up pilot studies, Phase II studies or abstracts that are part of large abstract books. If found, these would not have been influential.

[771] Dr. Prat added that the POSITA would also not recommend to a patient that they should double their prescribed dose (20 mg to 40 mg) and simultaneously reduce the frequency of their injections. Dr. Prat explained, among other reasons, that unless it will increase efficacy, patients should be treated with the lowest dose.

[772] Dr. Prat agreed that there was general motivation to look for new treatments for MS, including oral treatments. Dr. Prat agreed that he had not referred to the CORAL study in his report, but he was aware of it. Dr. Prat acknowledged that oral treatments of glatiramer acetate were explored in the CORAL study and were not successful. Dr. Prat explained that by modifying glatiramer acetate and making it more stable, an oral dose may be possible and a POSITA would be motivated to pursue this.

[773] Dr. Prat acknowledged that injection site related lipoatrophy was relatively common but stated that it was an unusual and infrequent reason for discontinuing glatiramer acetate treatment. He disagreed that lipoatrophy had a significant psychological impact, although agreed that for some patients there would be some impact. Although the Copaxone label states that there is no treatment for lipoatrophy, Dr. Prat noted that he was aware that plastic surgery was an option. He did not say that he had recommended or resorted to plastic surgery for any patient.

[774] Dr. Prat acknowledged that injection site reactions are the most frequent adverse reactions, but noted that this was true of all injectables, but it was much less so for glatiramer acetate relative to the other DMTs. Dr. Prat stated that there was more concern about skin reactions associated with interferon injections. Dr. Prat noted that he did not observe problematic reactions to Copaxone in clinical practice. He also noted that Dr. Green's footnote reference to Edgar 2004 (in Dr. Green's report) relied on by Pharmascience was derived from a paper about acupuncture. Dr. Prat added that there was only a passing mention of lipoatrophy in Caon 2009.

[775] Dr. Prat explained that the prior art disclosed that daily injections were important for maintaining sufficient anti-inflammatory cells activated and available to enter patients' nervous system. The POSITA would not be motivated to reduce injection frequency and potentially counter this positive effect.

[776] Dr. Prat stated that it would be far more than the routine work of a clinician to arrive at the invention. Dr. Prat explained that a doctor would not be able to advise a patient to take 40 mg

or to prescribe this until a 40 mg glatiramer acetate product was approved for use and, as of 2009, there was no such approval in Canada. To get approval, a clinical trial would be required.

[777] Dr. Prat stated that if a new dosing regimen were sought, there were many other solutions to explore, which were not predictable based on the prior art. For example, to avoid injections, a POSITA would look to a different active ingredient or to modify glatiramer acetate to allow oral administration. To address lower frequency of glatiramer acetate, a patch or a sustained release injectable formulation could be pursued.

[778] Dr. Prat noted that there was little motivation to find a new dosing cycle. He again noted that in 2009 the POSITA was aware that 20 mg daily remained the optimal dose. However, to the extent that the POSITA sought to vary the dosing cycle of glatiramer acetate, there were other options – e.g., 30 mg, 50 mg, 75 mg and variations on the schedule. Nothing in the prior art pointed to three times a week.

D. *The '802 Patent is Not Obvious*

[779] The legal principles guiding the assessment of obviousness are set out above at Part XX and have been applied.

[780] With respect to the evidence, contrary to Pharmascience's submission, I do not find that the evidence of Drs. Day and Prat should be disregarded or discounted and that the evidence of Dr. Green should be determinative on the key issues.

[781] Pharmascience suggests that Dr. Prat is less qualified than Dr. Green because Dr. Prat explained that he spends 70% of his time as a lab scientist and clinical neurologist and has not focussed on clinical studies of humans. Pharmascience submits that, therefore, Dr. Prat's opinions on the clinical trials (e.g., Comi 2008, Khan 2008, Caon 2009, and Flechter 2002) should be given less weight than those of Dr. Green, who is a specialized clinician.

[782] Pharmascience also submits that Dr. Prat's opinion on obviousness should be given little weight because he was misinstructed on the "obvious to try" test and he failed to consider that the POSITA can bridge the differences using the common general knowledge and information gathered as the result of a reasonably diligent search. Pharmascience also submits that Dr. Prat erred in taking the approach that the only relevant prior art is a Phase III clinical trial.

[783] Neither Dr. Day nor Dr. Prat are sceptics. Dr. Day is a biostatistician and, of course, his role was to assess the statistical significance of studies. His opinion does not make him a sceptic. Dr. Prat's evidence was candid and consistent. He took a balanced approach to his responses. He offered context even when he was discouraged to do so. He provided explanations about why he disagreed with Dr. Green and explained why some abstracts and reports would provide guidance and others would not.

[784] Dr. Green also provided clarifications, explanations and additional context for his opinions. Some of his opinions on key issues were more nuanced in his responses on cross-examination.

[785] As noted above, all the experts provided helpful and relevant evidence. However, as is typical, the experts do not agree on the key issues. As noted at the outset, I have considered all of the expert and factual evidence in its full context.

[786] However, there are several examples of the parties seeking to extract responses from the experts on specific points to support particular arguments. The arguments based on isolated responses have glossed over the thrust of the evidence. As a result of this approach, I have been required to very carefully review the evidence in its totality to determine if the experts were in fact supporting the particular argument.

[787] For example, Pharmascience suggests that Teva's expert, Dr. Morrow, agreed that the '437 Patent taught the use of 40 mg glatiramer acetate administered three times per week for the treatment of MS (i.e., what is claimed in the '802 Patent). The evidence relied on by Pharmascience relates to questions put to Dr. Morrow about the construction of the claims of the '437 Patent. Dr. Morrow agreed that claim 1 referred to periodic administration and that claim 13 added the essential element of daily administration. Dr. Morrow also agreed that the '437 Patent included a claim for 40 mg (claim 16). On cross-examination, Dr. Morrow acknowledged that it was possible that 40 mg three times per week would be covered by the claims of the '437 Patent. However, Dr. Morrow repeatedly stated that her answer was based only on the wording of claim 1, which did not set out a dosing schedule. In my view, this evidence cannot be relied on to suggest that the '437 Patent encompasses a three times weekly dosage of 40 mg of glatiramer acetate. As noted above, the '437 Patent is directed at daily administration of 20 mg for CIS patients. The examples do not address any other dosing regimen or the administration of 40 mg

glatiramer acetate. The silence of claims 1-12 regarding a dosing schedule does not support the argument that any possible schedule could work, particularly since the only schedule claimed is daily.

[788] Pharmascience also submits that injection site lipoatrophy resulting from injection of glatiramer acetate was so debilitating and irreversible that Dr. Prat's patients resorted to plastic surgery. Dr. Prat did not say that he had recommended plastic surgery to any patient. Dr. Prat's evidence was in response to the question of whether lipoatrophy was irreversible. Dr. Prat noted that plastic surgery would be an option. Moreover, his evidence is that, although lipoatrophy did occur in some patients, it was not a cause of lack of adherence to injections of glatiramer acetate.

[789] Pharmascience appears to put more emphasis on the "debilitating" effects of lipoatrophy as an injection site reaction than its expert Dr. Green does. Dr. Green referred to lipoatrophy once, noting that injection site reactions were "a component" of non-adherence. Pharmascience repeatedly points to Caon 2009, but there is only one line in that very short abstract regarding lipoatrophy.

[790] With respect to reduced frequency injections, contrary to Pharmascience's submission, Dr. Prat did not agree that a three times weekly dosing regimen of glatiramer acetate was preferable. Dr. Prat reluctantly agreed that if the only two options available were every other day or three fixed days a week, the three fixed days would be an improvement. Dr. Prat's opinion, which he clearly and repeatedly stated, was that daily administration was the better option for remembering to take the medication.

[791] I have not considered the outcomes of proceedings in foreign jurisdictions or the interest of the CIPO in the ‘802 Patent. As noted in *Mylan* at para 66:

> There is no doubt that the Court is not bound by the decisions of foreign courts dealing with corresponding patents, to say nothing of different patents. As this Court stated in *Eli Lilly v Apotex*, 2007 FC 455, at para 244 (aff’d 2008 FCA 44):
>
> > This Court is not bound by the decisions of foreign courts dealing with corresponding patents. In the words of the Federal Court of Appeal: “Although foreign patents may be practically identical, foreign law is unlikely to be so and must, in any case, be proved” (*Lubrizol Corp. v Imperial Oil Ltd.* (1992), 45 C.P.R.(3d) 449). These words are especially apt in the present matter which can be differentiated from what occurred in the United States on a number of grounds, including the nature of the proceedings, the evidence, and the burden of proof.

[792] The validity of the ‘802 Patent has been determined based on the jurisprudence and the evidence before this Court and nothing else.

[793] As noted, Pharmascience relies on a mosaic of the prior art to argue that the state of the art was that reduced frequency dosing regimens were known, 40 mg glatiramer acetate was known to be effective, and potentially more effective than 20 mg, and that Pinchasi 2007 disclosed and taught an every other day dosing regimen of 40 mg of glatiramer acetate. On this basis, Pharmascience submits that the small difference between the state of the art and the claims of the ‘802 Patent would be easily bridged by the POSITA who would be motivated to use the three times weekly dosing regimen to address injection site reactions and provide an easy to remember regimen to improve patient adherence.

[794] I do not agree with Pharmascience's depiction of the state of the art in 2009. The starting point in assessing obviousness is not that 40 mg glatiramer acetate every other day was effective to treat symptoms of MS.

[795] I find that Pharmascience and Dr. Green have overstated the teaching of the prior art they rely on.

[796] First, the prior art relied on by Pharmascience would not all have been found by the POSITA, as it was not all found by Dr. Green in his search. Notably, Dr. Green stated that he did not turn up the FDA SBOA, Khan 2008, Caon 2009 or Devonshire 2006. Dr. Green noted that he was not aware of the FDA SBOA or Flechter 2002 in 2009. Dr. Green also agreed that the POSITA would not look at Devonshire 2006.

[797] Second, even if all this prior art were found by the POSITA, the POSITA would rely on their expertise to read this art with a critical eye, make the distinction between small pilot studies, Phase II studies and Phase III studies, and know that some clinical studies are more reliable and informative than others.

[798] Dr. Day explained why certain studies teach more than others based on how they are conducted and how the results are portrayed.

[799] Dr. Selchen also explained the classes of evidence ranging from case reports and opinion pieces to Class 1 evidence of Phase III, double-blind clinical trials, noted to be the gold standard by all the experts.

[800] Dr. Prat also noted the several classes of evidence. Dr. Prat explained that abstracts are simply short summaries and that an abstract with a high number shows that it is one of at least that many abstracts presented and, as a result, would not be at the top of a POSITA's reading list.

[801] Third, I agree with Teva that Pharmascience has not explained how or why the POSITA would regard these pieces of prior art together in a mosaic to lead to the invention. However, even if the POSITA was handed this mosaic, it does not lead them directly to the subject matter of the claims. Contrary to Dr. Green's submission, it is not a matter of simple deduction to move from 20 mg daily, or even 20 mg every other day, to 40 mg three times weekly.

[802] As noted in *Servier* at para 254:

> As acknowledged by Servier, a mosaic of prior art may be assembled in order to render a claim obvious. Even uninventive skilled technicians would be presumed to read a number of professional journals, attend different conferences and apply the learnings from one source to another setting or even combine the sources. However, in doing so, the party claiming obviousness must be able to demonstrate not only that the prior art exists but how the person of ordinary skill in the art would have been led to combine the relevant components from the mosaic of prior art. This case is a good example.

[803] With respect to reduced frequency administration, as Dr. Green acknowledged, he was not even aware of the FDA SBOA in 2009. This document would not be found by the POSITA and, if found, would not teach anything about the impact of reduced frequency injections.

[804] Flechter 2002 indicated that 20 mg every other day was "probably" as effective as daily. Dr. Green admitted on cross-examination that he did not know about Flechter 2002 in 2009.

[805] Pharmascience was critical of Dr. Prat's assessment of Flechter 2002, noting that it exposed an error in Flechter 2002 regarding the calculation of the relapse rate reported for every-other-day patients. Pharmascience submitted that once corrected, Dr. Prat's criticism of Flechter 2002 could not be maintained, nor could his criticism of the cross-study comparison. However, Dr. Prat stated that he assessed the report as he found it. He acknowledged that if the calculation of the two-year relapse rate was as stated by Pharmascience (after its recalculation) the two relapse rates would be similar.

[806] Regardless, Dr. Prat's key concern about Flechter 2002 was that it reported on an investigatory study with insufficient data to support its "suggestion" that 20 mg glatiramer acetate every-other-day is as effective as glatiramer acetate daily.

[807] With respect to Khan 2008, the experts agreed that Dr. Khan was a highly regarded scientist. However, this does not automatically result in finding that every short article written by Dr. Khan would be found, read, and/or guide the POSITA. The abstract was less than one page long and reported on an investigatory study of only 30 patients comparing 20 mg daily and every

other day. As Dr. Prat noted, Khan 2008 was one of at least 900 abstracts presented at a three day conference of 5,500 participants and, as a result, would not have been brought to the attention of all those in attendance. Dr. Prat added that Khan 2008 would not be common general knowledge of the POSITA. Caon 2009 was also a less than one page abstract that reported on the same study of 30 patients. Dr. Prat described both Khan 2008 and Coan 2009 as "underpowered".

[808] Even assuming that the POSITA found these very short abstracts, they would read them with a discerning eye to reveal that both reported on the same investigatory study of 30 patients.

[809] Comi 2008 was acknowledged by all the experts to be a well-designed Phase III study conducted to confirm the results of the Phase II results (reported by Cohen 2007). All agree that it showed that 20 mg daily and 40 mg daily were equally effective, including with respect to safety and tolerability. All agree that Comi 2008 noted that there appeared to be a "trend" to earlier onset of action for the 40 mg dosage in the first three months, but this did not endure in the longer term. Dr. Green's reliance on Comi 2008 to assert that the 40 mg is potentially more effective ignores that after the three-month mark, the "trend" was not observed and, in the longer term, the study shows that 40 mg is simply equally effective.

[810] Dr. Prat explained that the FORTE Phase III study showed that 40 mg daily resulted in an increase of adverse effects compared to 20 mg daily. He noted that Professor Comi's presentation at the World Congress disclosed this increase in adverse events as "statistically significant compared to GA 20mg" and "the difference [was] mainly due to Injection Site

Reactions". The presentation also disclosed that there were "increased treatment discontinuation due to injection site reactions with the higher [40mg] dose".

[811] The POSITA who reviewed Comi 2008 in its entirety would not conclude that 40 mg was better than 20 mg, only that they were equally effective. The POSITA would also be alert to the possibility of adverse side effects of the 40 mg dose.

[812] Pharmascience and Dr. Green heavily rely on Pinchasi 2007 as the state of the art and as motivation for the subject matter of the claims of the '802 Patent.

[813] In my view, it is doubtful that the POSITA would look for patent applications. However, if the POSITA did turn up Pinchasi 2007, the POSITA would assess its teachings based on the fact that it was simply an application that was not approved.

[814] Dr. Green described three messages from Pinchasi 2007 (as noted above). I do not agree that the POSITA would take away the same messages or weave the other art in the manner suggested to bolster Pinchasi 2007.

[815] If the POSITA reviewed Pinchasi 2007 along with Cohen 2007 and Comi 2008 as Dr. Green suggests, the POSITA would not likely conclude that it teaches that 40 mg could be administered every other day and would be efficacious. If an unapproved patent application can be regarded as teaching anything, Pinchasi 2007 did not teach – even given its reference to Cohen 2007 – that 40 mg had increased efficacy over 20 mg. Nor did Pinchasi 2007 teach an

every other day administration. Although Pinchasi 2007 noted the results of Cohen 2007, it did not set out the additional results of Comi 2008 regarding the adverse side effects of 40 mg. Moreover, if the POSITA read Pinchasi 2007, the POSITA would know that the focus was on daily administration of 40 mg glatiramer acetate.

[816] As noted in the description of the prior art above, Pinchasi 2007 describes its invention as "periodically administering" 40 mg of glatiramer acetate to alleviate the symptoms of RRMS. In one embodiment, the periodic administration is daily. In another embodiment, the periodic administration is every other day. In a further embodiment, the pharmaceutical composition is in the form of a sterile solution for once daily administration. The claims include a claim for daily administration and a claim for every other day administration. However, the only example is based on the FORTE Phase II study, which compared 40 mg and 20 mg administered daily as reported by Cohen 2007. There is no data in Pinchasi 2007 to support an every other day administration of 40 mg glatiramer acetate.

(1) The State of the Art

[817] Based on the review of the prior art, and all the expert evidence, I find that the state of the art in 2009 was that:

- 20 mg glatiramer acetate daily was used to treat RRMS and CIS;
- 20 mg glatiramer acetate every other day had been explored in small, pilot studies without reliable results, only suggestions based on a small sample size (Flechter 2002, Khan 2008 and Caon 2009) which do not support any

conclusion or teaching of the effectiveness of every-other-day administration of glatiramer acetate;

- Comi 2008 (FORTE Phase III) demonstrated that 40 mg glatiramer acetate was equally effective as 20 mg. A trend towards earlier onset of action was "suggested" for 40 mg. An increase in adverse reactions, mainly due to injection site reactions, was reported for 40 mg;
- Patient adherence to their DMT was a general concern for all DMTs and dosing schedules;
- There were several factors at play regarding patient adherence, including injection site reactions;
- The interferons were different compounds, all with different prescribed dosing schedules; and,
- Pinchasi 2007 was a patent application – that was not approved – that focussed on 40 mg daily for RRMS and relied on Cohen 2007 (FORTE Phase II).

[818] The experts all agreed that not all prior art is common general knowledge.

[819] I accept Dr. Prat's view that Flechter 2002, Khan 2008 and Caon 2009 were not part of the common general knowledge.

[820] I also accept Dr. Prat's opinion that it was not common general knowledge that 40 mg daily was potentially more effective than 20 mg daily. As noted, the Phase II and Phase III results reported only a trend to faster onset of action at the three-month mark.

[821] Contrary to Pharmascience's position, it was not common general knowledge that decreasing the frequency of injections would increase patient compliance and adherence. All the experts agreed that there were several factors at play regarding compliance and adherence.

[822] Dr. Green stated that "a component" of non-adherence and non-compliance was related to frequency of injection. He stated that it is "just standard common sense" that if you give less frequent administration of most drugs, enhanced compliance will result, especially if there is a convenient dosing schedule that is easy for a patient to remember. However, Devonshire 2006 and Treadaway 2009 do not support this supposition. Dr. Prat repeatedly noted that forgetting to take the DMT is the common reason for non-adherence.

(2) Differences between the State of the Art and the Subject Matter of the Claims

[823] There were material differences between the state of the art and the subject matter of the claims.

[824] As noted above, the starting point in assessing the differences is not 40 mg every other day (Pinchasi 2007); rather, it is 20 mg daily as the optimal dosage. The POSITA would also be aware that 40 mg had been demonstrated to be as effective as 20 mg.

(3) Not Obvious to Try

[825] The POSITA using the common general knowledge and information gathered from a reasonably diligent search (*Ciba* at para 62) would not come directly and without difficulty to the subject matter of the claims of the ‘802 Patent.

[826] As noted above, Pharmascience has not explained how or why the POSITA would combine the prior art relied on. However, even if the POSITA did so, it would not point them to try to obtain the invention (*Hospira* at para 86).

[827] As noted by Dr. Prat, even if the POSITA supplemented the common general knowledge with the results of a reasonably diligent search, the POSITA would not turn up several of the articles relied on or other articles not already identified by Dr. Green to support the view that 40 mg three times a week was the way to go. Dr. Green’s search revealed over 1,300 articles, of which a handful were relied on and, as found above, several would not guide the POSITA and would not create a mosaic for the POSITA to support Pharmascience’s position.

[828] Contrary to Pharmascience’s submission, Dr. Prat was not misinstructed on the test for obviousness. But, even if he were, it is the Court’s task to determine if the test established in *Sanofi* and elaborated on in subsequent jurisprudence has been met, based on the evidence. The Court appreciates that the obvious to try test is informed by several factors, one of which is whether it was self-evident that the invention would work (*Hospira* at para 90).

[829] The evidence does not establish that it was more or less self-evident for the POSITA to try to obtain the invention of 40 mg glatiramer acetate three times weekly, or that it was self-evident that this would work to alleviate the symptoms of RRMS.

[830] Bridging the differences between the state of the art and the subject matter of the claims required inventive ingenuity.

[831] As Dr. Prat emphasized, nothing taught that 40 mg administered periodically or three times a week would be effective. In addition, the general approach is to not increase the dosage. 20 mg daily was considered to be the optimal dosage, despite no studies supporting how the 20 mg dosage was arrived at years ago.

[832] The art did not provide motivation to both change the dose and the frequency of administration. Comi 2008 confirmed that 20 mg and 40 mg were equally effective. The suggestion or trend to a faster onset of action for the 40 mg dose would not motivate the POSITA given that these results did not continue for the longer term and there is no evidence or suggestion that such a result would occur in an every other day dose.

[833] The concerns about injection site reactions were acknowledged by the experts, but are not key motivating factors for reduced injection frequency. Dr. Prat noted that this concern would motivate the POSITA to consider non-injectables. It would not motivate the POSITA to consider a higher dose as a lower dose is always preferred if effective.

[834] In addition, Dr. Prat noted that Comi 2008, which was more authoritative, reported adverse reactions for 40 mg. Dr. Prat stated that a POSITA would not increase the dosage if it would increase adverse reactions.

[835] Dr. Morrow had indicated that if a patient had a concern about needles, fewer injections were not the solution, rather a different approach. Dr. Prat also noted that some patients have a concern about self-injections but it is short lived.

[836] As noted above, Dr. Green also agreed that injection site reactions were "a component" contributing to non-adherence.

[837] Dr. Prat acknowledged that the '802 Patent stated that in clinical trials "injection-site reactions were seen to be the most frequent adverse reactions and were reported by the majority of patients receiving [glatiramer acetate]". However, this reaction was in comparison to injections of placebo.

[838] The Rebif regimen of three times weekly would not motivate the POSITA given that all agree that interferons are different – even if no one can explain how – and the other interferons have different dosing regimens.

[839] Dr. Prat explained that if there were motivation to move away from injections, an oral formulation could be explored. He acknowledged the failure of the CORAL study and noted that glatiramer acetate could be modified to develop an oral formulation. Other approaches that could

be pursued to avoid injections altogether included a sustained release injectable formulation or a patch. Dr. Prat noted that there was little motivation to find a new dosing cycle.

[840] With respect to the effort required to obtain the invention, Dr. Green's suggestion that it would be a simple matter to discuss the dosing regimen with a patient is based on his view that the starting point was 40 mg every other day. Dr. Green acknowledged that in 2009, a patient would have to take two 20 mg injections in order to have a 40 mg dose every other day or three times weekly because 40 mg was not available. In my view, two injections would clearly defeat the purpose of reducing injection frequency. In addition, Dr. Green's suggestion that a patient could combine two 20 mg doses in a syringe appears to be beyond the skills or desire of a patient.

[841] Dr. Green also agreed that a clinical study would be required to evaluate whether 40 mg three times weekly would be effective. When asked why it would be routine work to administer 40 mg outside of a clinical study, Dr. Green responded that it would "make sense" to posit the use of a three times per week schedule. Dr. Green drew a distinction between routine work and routine clinical work.

[842] With respect to this off-label use, Dr. Green acknowledged that he had given a different opinion in other proceedings, where he stated it would not be appropriate to prescribe 20 mg every other day, as that would be off-label and only appropriate in clinical study (i.e., not routine clinical work). Dr. Green also agreed that he would not advise his patients to skip doses and would not advise patients to take Copaxone 40 mg three times a week until it was approved.

[843] I place more reliance on the evidence of Dr. Prat who stated that a clinical trial would be required and that a neurologist could and would not use 40 mg off-label, even if it were available.

[844] With respect to the history of the invention, Teva did not provide evidence from the inventors. Contrary to Pharmascience's submission, the Court does not draw an adverse inference from this. Dr. Kreitman explained the work undertaken by Teva.

[845] Dr. Kreitman stated that Teva conducted several studies to explore different possible improvements to Copaxone. With respect to the higher dose, lower frequency administration regimen which ultimately led to Copaxone 40 mg three times a week, Dr. Kreitman explained that her team at Teva evaluated several dosing regimens (including 40 mg every other day, 40 mg three times per week, 35 mg three times per week, and 40 mg once or twice per week) before the decision was made to proceed with the clinical trial of 40 mg three times a week (the GALA trial).

[846] Dr. Kreitman acknowledged that Teva did not have supporting clinical evidence for the contemplated reduced-frequency dosing regimens, but had pre-clinical evidence.

[847] Pharmascience suggests that Teva pursued the invention because its other patent was soon expiring and because it feared that the generic version of 20 mg glatiramer acetate would be used three times per week rather than the 40 mg product. Dr. Kreitman acknowledged that the other patent would expire, but with respect to the possible generic use of 20 mg, she explained

that she was copied on an email sent by another person who relayed a concern about use of the generic product.

[848] Contrary to Pharmascience's submission, I do not find that Teva pursued the GALA trial only to confirm what was already known.

[849] In conclusion, the subject matter of the claims – 40 mg glatiramer acetate administered three times a week to treat RRMS, and alleviate symptoms as measured in different ways – was not obvious. The material differences between the state of the art and the subject matter of the claims could not be easily bridged by the POSITA using their common general knowledge and additional information gleaned from a reasonably diligent search. It was not self-evident to try 40 mg of glatiramer acetate three times weekly or that the 40 mg three times weekly dose would work; there were other possible solutions to address patient adherence if that were a motivating concern; and, there was no motivation to simultaneously increase the dose, given that the increased dose had not been shown to be more effective, and reduce the frequency of administration.

XXV. Is the '802 Patent Invalid due to Lack of Utility or Sound Prediction of Utility?

A. *Teva's Submissions*

[850] Teva submits that Pharmascience has not met its burden to establish inutility on a balance of probabilities as it has not adduced any evidence to show that the invention was not useful. Nor

has Pharmascience adduced evidence to establish that the utility of the invention was not soundly predicted and supported by the information disclosed in the ‘802 Patent and the art incorporated by reference.

[851] Teva submits that the actual utility of the invention has not been put into dispute. Moreover, the subject matter of the claims has utility. Teva notes that glatiramer acetate 40 mg has been approved for use as a subcutaneous injection administered three times per week for treating RRMS. Teva submits that this approval would not have been granted without evidence of efficacy. It is also clear from the evidence that doctors in Canada prescribe Copaxone 40 mg in accordance with the asserted claims (i.e., to treat RRMS). Teva questions why Pharmascience would want to replicate the invention if it were not useful.

[852] Teva argues that Pharmascience’s attack on the utility of the ‘802 Patent appears to be more about the lack of disclosure of the utility. Teva submits that the disclosure requirement is to ensure that the invention can be put into practice. The utility requirement is satisfied without any disclosure provided the test set out in *AstraZeneca Canada Inc v Apotex Inc*, 2017 SCC 36 at para 53 [*AstraZeneca*] is met. Teva submits that it is; the subject matter is capable of a practical purpose, which is to alleviate symptoms of RRMS.

[853] Teva submits that all that is required for sound prediction is a “prima facie reasonable inference of utility” (*Eli Lilly Canada Inc v Novopharm Limited*, 2010 FCA 197 at para 85).

[854] Teva notes that the ‘802 Patent includes a detailed description of the Phase III clinical study, including its protocol, mid- and end-points, and efficacy and safety results of 40 mg three times per week, all of which provide the prediction for the basis of at least a scintilla of utility. The patent also incorporates 18 references to support the invention. Teva submits that this disclosure, coupled with the 18 references, is more than enough to meet the test.

[855] Teva further submits that the soundness of a line of reasoning can be assessed by determining how the POSITA would interpret and accept the logic presented in the patent’s specification (*Bell Helicopter Textron Canada Limitée v Eurocopter, société par actions simplifiée*, 2013 FCA 219 at para 154 [*Eurocopter*]). Teva notes that Pharmascience did not question the experts about whether they would accept the logic in the ‘802 Patent.

[856] Teva adds that Pharmascience’s expert, Dr. Green, did not provide any opinion on whether this disclosure fails to meet the requirements for utility.

[857] Teva submits that it had a sound line of reasoning, including extensive internal research into glatiramer acetate, including: pre-clinical studies showing efficacy in reduced frequency dosing; proposing, planning and designing a detailed Phase III clinical study on the efficacy of 40 mg three times per week; and, commencing the clinical trial on RRMS patients.

[858] Teva submits that Dr. Kreitman described a process that was clearly not routine. Dr. Kreitman explained that Teva’s decision to develop the 40 mg three times per week product was based on the prior studies of glatiramer acetate, the studies to show the safety of 40 mg and

the work done to understand the mechanism of action of Copaxone. Dr. Kreitman noted Teva's pre-clinical evidence and that it had conducted animal studies before August 2009.

[859] Teva argues that, despite filing no evidence, Pharmascience simply asserts that the requirements of a demonstration or sound prediction of utility as of the filing date of the '802 Patent are not met and points to a confusing exchange with Dr. Prat on cross-examination.

[860] Teva submits that Pharmascience cannot rely on Dr. Prat's responses to meet its burden to demonstrate lack of utility or lack of sound prediction. Dr. Prat's opinion was on the validity of the '802 Patent. Dr. Prat clearly stated that he was not familiar with the legal tests for utility or the notion of reasonable inferences as sought by Pharmascience. Dr. Prat provided his responses based on the common general knowledge as of August 2009, which is not the relevant date for the utility analysis. Dr. Prat stated that he was not aware of what may have been done by Teva between August 2009 and August 2010.

[861] Teva also disputes Pharmascience's suggestion that the outcome of a phase III clinical trial cannot be predicted until all the data is compiled and, therefore, Teva could not soundly predict utility. Teva notes that Pharmascience took the contrary view with respect to the validity of the '437 Patent.

[862] Teva submits that the Supreme Court of Canada has rejected the notion that patents can be invalidated because a phase III clinical trial had not been completed, noting that the requirements for sound prediction of utility are not at the same level as the requirements for

regulatory approval and that the doctrine of sound prediction recognizes that further work will be done (*Apotex Inc v Wellcome Foundation Ltd*, 2002 SCC 77 at para 77 [*Wellcome*]).

B. *Pharmascience's Submissions*

[863] Pharmascience argues that if the '802 Patent is not obvious due to the state of the prior art, then Teva cannot resort to the prior art that it discounts or rejects to support the utility or sound prediction of utility of the '802 Patent. More particularly, Pharmascience argues that if Teva is correct regarding the state of the prior art (i.e., as not teaching 40 mg every other day), then Teva has no prior art to rely on before the filing date to soundly predict the utility of a three times per week dosing regimen of 40 mg of glatiramer acetate.

[864] Pharmascience argues that there was no demonstration of use, i.e., no supporting data regarding 40 mg three times per week. Pharmascience adds that Teva has not done or disclosed any testing to support a sound prediction as of August 2010 that 40 mg of glatiramer acetate three times per week would be effective to treat RRMS.

[865] Pharmascience notes that no data from the GALA trial was available until months later and there was no factual basis available to Teva to make any prediction regarding the claimed uses. Pharmascience notes that the first patient was enrolled in the GALA trial in late June 2010. Pharmascience submits that Teva could not possibly have demonstrated utility by August 19, 2010 and, as a result, could not have soundly predicted the utility of 40 mg glatiramer acetate three times per week for the treatment of RRMS in a human patient.

[866] Pharmascience points to Dr. Prat's responses on cross-examination, including his statement that "I don't see why the skilled person would infer that 40 mg three times a week would work or would be better than 20 mg every day".

[867] Pharmascience describes the example in the '802 Patent as "prophetic" as it refers to a future study (GALA), which would not, once completed, provide any data regarding the comparative efficacy of 40 mg three times per week to other dosage regimens because the comparator is to placebo.

[868] Pharmascience also submits that Teva has a "fatal disclosure problem". Pharmascience submits that Teva cannot rely on Dr. Kreitman's evidence describing Teva's internal *in vitro* and/or animal testing related to Copaxone and the TV-5010 glatiramoid product that may have led Teva to believe that the products could be administered less frequently than once per day because this was not disclosed in the '802 Patent. Pharmascience adds that there is no reason to believe that the TV-5010 testing could have supported any prediction about glatiramer acetate.

[869] Pharmascience also suggests that Dr. Kreitman's evidence is inconsistent with a presentation made to Teva's CEO in June 2009, which indicated that there was no supporting data available for the three times per week 40 mg dosing regimen.

C. *Principles from the Jurisprudence*

[870] The Supreme Court of Canada clarified the test for utility in *AstraZeneca* and the distinction between the *Patent Act* requirements in section 2 (regarding usefulness) and subsection 27(3) (regarding disclosure) at paras 42-43:

> [42] Section 27(3) of the *Act* provides that in the specification, a "patentee must describe the invention 'with sufficiently complete and accurate details as will enable a workman, skilled in the art to which the invention relates, to construct or use that invention when the period of the monopoly has expired'" (*Whirlpool*, at para. 42, quoting *Consolboard*, at p. 517).
>
> [43] There is a difference between the requirement in s. 2 that an invention be "useful" and the requirement to disclose an invention's "operation or use" as per s. 27(3). As explained by Dickson J. (as he then was) in *Consolboard*, the former is a "condition precedent to an invention" and the latter a "disclosure requirement, independent of the first":
>
> > . . . the Federal Court of Appeal erred also in holding that s. 36(1) [now s. 27(3) and (4)] requires distinct indication of the real utility of the invention in question. There is a helpful discussion in *Halsbury's Laws of England* (3rd ed.), vol. 29, at p. 59, on the meaning of "not useful" in patent law. It means "that the invention will not work, either in the sense that it will not operate at all or, more broadly, that it will not do what the specification promises that it will do". There is no suggestion here that the invention will not give the result promised. . . .
> >
> > . . . the Federal Court of Appeal has confused the requirement of s. 2 of the *Patent Act* defining an invention as new and "useful", with the requirement of s. 36(1) [now s. 27(3)] of the *Patent Act* that the specification disclose the "use" to which the inventor conceived the invention could be put. The first is a condition precedent to an invention, and the second is a disclosure requirement, independent of the first. [Emphasis added]

(*Consolboard*, at pp. 525 and 527)

While the above passage uses the word "promise", it does not refer to, nor does it embody, the Promise Doctrine.

[871] In *AstraZeneca* at paras 54-58, the Court set out the test for utility and reiterated that utility must be either demonstrated or soundly predicted:

> [54] To determine whether a patent discloses an invention with sufficient utility under s. 2 , courts should undertake the following an analysis. First, courts must identify the subject-matter of the invention as claimed in the patent. Second, courts must ask whether that subject-matter is useful — is it capable of a practical purpose (i.e. an actual result)?
>
> [55] The Act does not prescribe the degree or quantum of usefulness required, or that every potential use be realized — a scintilla of utility will do. A single use related to the nature of the subject-matter is sufficient, and the utility must be established by either demonstration or sound prediction as of the filing date (*AZT*, at para. 56).
>
> [56] The utility requirement serves a clear purpose. To avoid granting patents prematurely, and thereby limiting potentially useful research and development by others, the case law has imposed a requirement that an invention's usefulness be demonstrated or soundly predicted at the time of application, rather than at some later point. This ensures patents are not granted where the use of the invention is speculative. What matters is that an invention "be useful, in the sense that it carries out some useful known objective" and is not merely a "laboratory curiosity whose only possible claim to utility is as a starting material for further research" (*Re Application of Abitibi Co.* (1982), 62 C.P.R. (2d) 81 (Patent Appeal Board and Commissioner of Patents), at p. 91).
> [57] The application of the utility requirement in s. 2, therefore, is to be interpreted in line with its purpose — to prevent the patenting of fanciful, speculative or inoperable inventions.
> [58] Even though utility of the subject-matter is a requirement of patent validity, a patentee is not required to disclose the utility of the invention to fulfill the requirements of s. 2. As was stated by Dickson J. in *Consolboard*:
>
> > . . . I do not read the concluding words of s. 36(1) [now s. 27(4)] as obligating the inventor in his

> disclosure or claims to describe in what respect the invention is new or in what way it is useful. He must say what it is he claims to have invented. [p. 526]

See also *Teva*, at para. 40.

[872] In *Wellcome* at para 70, the Supreme Court of Canada set out the requirements of sound prediction: a factual basis for the prediction; an articulable and "sound" line of reasoning from which the desired result can be inferred from the factual basis; and, proper disclosure. The Court added, with respect to disclosure, that "[n]ormally, it is sufficient if the specification provides a full, clear and exact description of the nature of the invention and the manner in which it can be practised."

[873] The Court noted at para 77:

> 77 The appellants take issue with the trial judge's conclusion. In their factum (though not in oral argument), they argue that utility must be demonstrated by prior human clinical trials establishing toxicity, metabolic features, bioavailability and other factors. These factors track the requirements of the Minister of Health when dealing with a new drug submission to assess its "safety" and "effectiveness". See now: *Food and Drug Regulations*, C.R.C. 1978, c. 870, s. C.08.002(2), as amended by SOR/95-411, s. 4(2), which provides in part:
>
> > A new drug submission shall contain sufficient information and material to enable the Minister to assess the safety and effectiveness of the new drug. . . .
>
> The prerequisites of proof for a manufacturer who wishes to market a new drug are directed to a different purpose than patent law. The former deals with safety and effectiveness. The latter looks at utility, but in the context of inventiveness. The doctrine of sound prediction, in its nature, presupposes that further work remains to be done.

[874] In *Eurocopter* at paras 154-155, the Court of Appeal noted that the law was not settled regarding whether there was an enhanced disclosure requirement where sound prediction was relied on. The Court noted that a contextual approach is required in each case. The Court explained that the soundness of the line of reasoning may be assessed from the perspective of the POSITA who, with their common general knowledge, would determine whether to accept the logic presented. The Court stated at paras 152-155:

> [152] In my opinion, the factual basis, the line of reasoning and the level of disclosure required by the doctrine of sound prediction are to be assessed as a function of the knowledge that the skilled person would have to base that prediction on, and as a function of what that skilled person would understand as a logical line of reasoning leading to the utility of the invention.
>
> [153] Where the factual basis can be found in scientifically accepted laws or principles or in information forming part of the common general knowledge of the skilled person, then no disclosure of such factual basis may be required in the specification. On the other hand, where the factual basis is reliant on data which does not form part of the common general knowledge, then disclosure in the specification may indeed be required to support a sound prediction.
>
> [154] As noted in the *Manual of Patent Office Practice* issued by the Canadian Patent Office (at paras. 12.08.04*b* and 12.08.04*c*), since a sound line of reasoning is directed to a skilled person, those elements of the doctrine of sound prediction that would be self-evident to that person in view of the common general knowledge need not be explicitly disclosed in the specification. The soundness of a line of reasoning can also be effectively assessed by asking whether the skilled person would accept the logic presented in the specification and derive from the sound prediction as a whole an expectation that the invention will provide the promised utility.
>
> [155] As a result, where the sound prediction is based on knowledge forming part of the common general knowledge and on a line of reasoning which would be apparent to the skilled person (which is often the case in mechanical inventions), the requirements of disclosure may readily be met by simply describing the invention in sufficient detail such that it can be practiced. A contextual approach is thus appropriate in each case.

[875] The principles from the jurisprudence can be summarized as follows:

- The utility of a patent must be established by either demonstration or sound prediction as of the filing date.

- The test for utility requires the Court to first identify the subject matter of the invention and, second determine whether the subject matter is useful – i.e., capable of a practical purpose.

- A scintilla of utility is sufficient.

- Sound prediction requires: a factual basis for the prediction; a sound line of reasoning from which the derived result can be inferred from the factual basis as of the date of the patent application; and proper disclosure (a full, clear and exact description of the nature of the invention and the manner in which it can be practised).

- The requirements of subsection 27(3) for disclosure are distinct from the requirements of utility. Subsection 27(3) does not require that the utility of the invention be disclosed. Subsection 27(3) is satisfied if the POSITA can produce the subject matter using the instructions or description in the disclosure.

D. *The ‘802 Patent is Not Invalid due to Lack of Sound Prediction of Utility*

[876] In applying the test for utility set out in *AstraZeneca*, the first step is to identify the subject matter of the invention. For the ‘802 Patent, the subject matter is 40 mg of glatiramer acetate three times weekly (with a day in between doses) to treat RRMS and alleviate a symptom of RRMS (measured in various ways). The next step is to determine whether this subject matter is useful, in the sense of being capable of a practical purpose.

[877] Although Teva submits that the patent is useful, otherwise Pharmascience would not want to replicate it, Teva did not demonstrate its utility as of the filing date. Teva does not dispute that no data was disclosed in the ‘802 Patent, rather Teva notes that the clinical trial was underway to confirm or test the results of earlier and smaller studies and relies on the references in the ‘802 Patent and Dr. Kreitman’s description of the extensive planning and past clinical trials to improve Copaxone.

[878] Where utility is not demonstrated, it must be soundly predicted. Pharmascience alleges but has not established that the ‘802 Patent lacked a sound prediction of utility. The evidence does not support the allegation.

[879] The ‘802 Patent discloses its reasoning for pursuing the reduced frequency regimen of 40 mg and refers to other studies, albeit small, as well as the Phase II and Phase III studies that demonstrated the effectiveness of 20 mg and 40 mg glatiramer acetate daily.

[880] The ‘802 Patent sets out the details of the GALA trial – a Phase III, multi-national, multi-center, double-blind randomized study of subjects with RRMS to assess the efficacy, safety and tolerability of 40 mg glatiramer acetate administered three times per week by injection compared to placebo. The objectives, design, inclusion and exclusion criteria, primary, secondary and exploratory endpoints, various outcome measures, statistical considerations and primary outcome measures are described.

[881] In the Discussion of the ‘802 Patent, it notes that a “significant drawback to [glatiramer acetate] therapy is the requirement of daily injections, which can be inconvenient”. The Discussion refers to several drawbacks to current glatiramer acetate therapy, including injection volume, drug degradation, and localised irritation. The Discussion also notes that, due to the pharmacokinetic behaviour of a drug, variation in the frequency of administration is unpredictable and requires empirical testing.

[882] As noted in *Wellcome* at para 77, the results of a clinical study are essential for regulatory approval, but the doctrine of sound prediction recognizes or “presupposes that further work remains to be done”.

[883] The GALA trial, as described in the ‘802 Patent, is that remaining work.

[884] Pharmascience argued, with respect to its allegation of obviousness, that Teva conducted the GALA trial to confirm what was already known. Now it turns that argument around to suggest that Teva did not know that the invention would be useful and there was no soundly

predicted utility. Although it was not known or obvious that 40 mg administered three times weekly would be an effective treatment for MS, in my view there is a sound prediction set out in the ‘802 Patent.

[885] The POSITA would review the ‘802 Patent and the details of the GALA trial, including its expected results, with the common general knowledge (as noted above to include that 20 mg daily was effective, that 40 mg daily was equally effective (Comi 2008) and that several factors, including injection site reactions, contributed to patient non-adherence), and would accept the logic presented – that 40 mg three times weekly would alleviate symptoms of RRMS (*Eurocopter* at 154-155). A scintilla of utility is all that is required and the POSITA would expect at least a scintilla of utility to treat RRMS based on the logic presented.

[886] The disclosure set out in the ‘802 Patent is more than sufficient to permit the POSITA to put the subject matter of the claims into practice.

[887] Pharmascience relies on the testimony of Dr. Prat on cross-examination and the testimony of Dr. Kreitman to support the allegation that there was no demonstrated or soundly predicted utility. Pharmascience argues that if the prior art it cited does not make the ‘802 Patent obvious, then that prior art cannot support the utility of the invention.

[888] Although evidence given on cross-examination can be used to establish such legal tests, it does not do so in the present case.

[889] As noted in *Pfizer Canada Inc v Apotex Inc*, 2017 FC 774 at para 373, the Court will be cautious to accept answers provided by experts on legal tests that exceed their mandate and expertise:

> [373] However I am unable to accept this evidence for several reasons. First, as Pfizer correctly pointed out, neither Drs. Bastin nor Steed were instructed on the law of anticipation, and neither was instructed on either disclosure or enablement. I am unable to see how the Court may confidently accept what is stated by a scientific expert witness when he or she has no understanding of the legal meaning of the words or concepts at issue.

[890] Pharmascience notes that the GALA protocol referred to Flechter 2002, Khan 2008 and Caon 2009, all of which Teva argued were not prior art and taught nothing. Although those small studies were not sufficient to support the allegation of obviousness, utility is a different analysis. For obviousness, these short abstracts on small studies would not all turn up in a search (and did not turn up in Dr. Green's search) and were not common general knowledge or part of a mosaic of prior art that the POSITA would combine to lead them to the invention. Pharmascience's expert, Dr. Green, agreed that he would not or did not change his practice based on these small studies. However, for the assessment of utility, these references are incorporated in the '802 Patent and can be considered by the POSITA in assessing the logic in the '802 Patent.

[891] Dr. Prat acknowledged that the GALA protocol cited Flechter 2002, Khan 2008 and Caon 2009 (which explored 20 mg daily vs 20 mg every other day) as support for the Phase III study. He explained that small trials such as these need to be confirmed by a Phase II and Phase III study, as noted by their authors. The GALA trial, while not proposing 20 mg every other day, sought to confirm the usefulness and effectiveness of a less frequent dosing regimen.

[892] With respect to its allegation of lack of sound prediction of utility, Pharmascience relies on Dr. Prat's response to its question whether – without any data from the GALA trial – the POSITA would infer that 40 mg three times a week would work. Dr. Prat responded that the POSITA would not have thought that: "I don't see why a skilled person would infer that 40 mg three times a week would work or would be better than 20 mg every other day".

[893] However, when Dr. Prat's testimony on this issue is considered in its totality, it shows that Dr. Prat was not opining on the test for utility as of the filing date. Dr. Prat stated that he did not understand the notion of a reasonable inference and that the questions were beyond his mandate and the opinion he had provided.

[894] Dr. Prat stated that no data had been presented on 40 mg administered every other day in the prior art. He noted that 20 mg daily was known and 40 mg daily was known. He added that there was nothing known about 40 mg every other day, and in that sense it was inventive, but added that the '802 Patent may have been based on data that was not disclosed to him.

[895] After stating that he was not familiar with the notion of reasonable inference, counsel for Pharmascience continued to seek Dr. Prat's view. The relevant parts of the exchange are set out below:

> Q. Okay. And the skilled person doesn't have any data because none is provided in the '802 patent. Okay? Has no data about three times a week. So I am asking you, putting yourself in the shoes of that skilled person, you would agree with me that based on the common general knowledge, such as it was as of August 2010, the skilled person without any data available could not make a reasonable inference that the dosing regimen of claim 1, three times a week every other

day, would be effective to treat RRMS in a human patient. There is no way the skilled person could reasonably come to that conclusion. You agree with that, don't you?

A. (Dr. Prat). I agree with that, no, not really. What I agree is that if I would be the skilled person looking at that application I would say, well, this is probably a waste of time because you have enough data supporting the fact we are not going to be using Copaxone. But if you want to go forward, I mean there is no data that prevents you to protect that concept. That is what I would say as a skilled person. I would say Teva is spending its money chasing ghosts because they had enough data supporting not to use 40 and not to go lower than once a day. Do you see what I mean?

Q. The skilled person would reasonably come to the view that there is no way for this. Teva you want to go off on a frolic of your own, go. But from the skilled person's point of view this is just not reasonable?

A. As I said – and you asked me as of 2010. I don't know what sort of pilot data Teva had or anyone had on 40 milligram every other day. Nothing has been presented on 40 milligram every other day even in the prior art. There is 20 milligram every other day. There is 40 milligram daily. But there is nothing on 40 milligram every other day. So in that sense I do believe that it was inventive, but maybe it was based on data that was not disclosed or that was not disclosed to me. I mean even now as a skilled person of 2009. Do you understand my point?

[896] Clearly, Dr. Prat was reiterating his opinion on the inventiveness of the ‘802 Patent.

[897] Dr. Prat was not asked whether the ‘802 Patent contained a factual basis or sound line of reasoning for the prediction that 40 mg three times weekly would alleviate symptoms of RRMS.

[898] Dr. Kreitman acknowledged that as of June 2009, Teva had no supporting clinical data for the contemplated reduced-frequency dosing regimens, but had pre-clinical evidence. The

regimens under consideration included: 40 mg every other day, 40 mg three times per week, 35 mg three times per week, and 40 mg once or twice per week.

[899] Dr. Kreitman explained that her team presented various dosing regimens to Teva's CEO and, ultimately, the CEO decided to move forward with a clinical trial of 40 mg three times a week. Dr. Kreitman referred to a presentation made in November 2008 which indicated that Teva had reason to believe that lower frequency administration, such as three-times-a-week, would be effective to treat MS and similar to daily administration.

[900] In conclusion, I find that the '802 Patent is not invalid for lack of sound prediction of utility.

XXVI. The Jurisdictional Issue – Can Teva rely on the *Regulations* to assert infringement by Pharmascience's Glatect 20 mg?

[901] As noted at the outset, Teva obtained NOCs to sell its glatiramer acetate product in Canada under the brand name Copaxone, in dosages of 20 mg and 40 mg. Teva listed the '437 Patent on the Patent Register, but only in respect of the 40 mg dosage. There are no patents listed on the Register in respect of the 20 mg dosage.

[902] Pharmascience obtained a NOC and has been selling its Glatect 20 mg product in Canada since August 2017.

[903] To obtain a NOC for a 40 mg dosage of glatiramer acetate (Glatect 40) Pharmascience filed a SNDS to the NDS it had submitted previously to obtain its NOC for Glatect 20 mg. Pharmascience refers to this as a "line extension". Pharmascience's SNDS directly or indirectly compares Glatect 40 mg to Copaxone.

[904] Pharmascience was not required to address the '437 Patent to obtain its NOC for Glatect 20 mg because the '437 Patent is not listed on the Patent Register in respect of the 20 mg dosage. However, Pharmascience was required to address the '437 Patent in respect of its Glatect 40 mg. Pharmascience served a NOA on Teva alleging that the making, constructing, using or selling of Glatect 40 mg will not infringe the '437 Patent and that the '437 Patent is invalid.

[905] Teva then commenced the T-2182-18 action pursuant to subsection 6(1) of the *Regulations* seeking a declaration that the making, constructing, using or selling of Glatect 20 and 40 mg by Pharmascience in accordance with the SNDS will infringe the '437 Patent.

[906] Pharmascience disputes Teva's ability to assert infringement against Glatect 20 mg under section 6 of the *Regulations* in the T-2182-18 action with respect to the '437 Patent.

[907] Pharmascience's motion to strike parts of Teva's original Statement of Claim was granted in part by Prothonotary Mireille Tabib (2019 FC 595) and its motion for a determination on a question of law with respect to the interpretation of the statutory provisions was dismissed (2019 FC 1394).

[908] On the motions and in this Action, Pharmascience does not contest that Teva has a reasonable cause of action pursuant to subsection 6(1) of the *Regulations* in respect of Glatect 40 mg. Pharmascience's position is that Teva does not have a valid cause of action pursuant to subsection 6(1) of the *Regulations* in respect of Glatect 20 mg.

[909] Pharmascience acknowledges that Teva would have a reasonable cause of action under section 55 of the *Patent Act* in respect of Glatect 20 mg, but argues that such an action cannot be joined to Teva's subsection 6(1) action in respect of Glatect 40 mg by reason of section 6.02 of the *Regulations*.

[910] On the motion to strike, Prothonotary Tabib noted that any rights of action for patent infringement are confined to those created by section 55 of the *Patent Act*, and those created by subsection 6(1) of the *Regulations*. Prothonotary Tabib emphasized that the *Regulations* contemplate that the rights of action conferred by subsection 6(1) be exercised within a strict procedural framework. Section 6.02 provides that, during the period of time defined in subsection 7(1) of the *Regulations*, these rights should not be combined with any other rights arising from the *Patent Act*.

[911] Prothonotary Tabib concluded that Teva did not have a reasonable cause of action under subsection 6(1) in respect of past or current infringement of the '437 Patent with respect to Glatect 20 mg. Prothonotary Tabib concluded that the inclusion of Teva's infringement action with respect to Glatect 20 mg as part of its subsection 6(1) action was prohibited by section 6.02 of the *Regulations*, and, as a result, some parts of the Statement of Claim were struck.

Prothonotary Tabib found that, otherwise, it was not plain and obvious that Teva's cause of action had no chance of success. Teva subsequently amended its Statement of Claim with respect to infringement.

[912] In the current Action, Teva submits that the outcome of this litigation will not have any impact on Glatect 20 mg because Pharmascience has already obtained a NOC. Teva also notes that it has not pursued any other litigation with respect to Glatect 20 mg.

[913] However, Teva continues to raise the jurisdictional issue regarding the scope of the *Regulations* and argues that Pharmascience's SNDS and its proposed combined Product Monograph for Glatect 20 and 40 mg will make additional changes to the 20 mg product, which bring it within the scope of the *Regulations.*

[914] Teva submits that Glatect 20 mg is a drug that will be made, used or sold in accordance with Pharmascience's SNDS. Teva submits that the SNDS is more than a "line extension" as it will make other changes with respect to the 20 mg product.

[915] Pharmascience continues to dispute Teva's ability to assert infringement of the '437 Patent against Glatect 20 mg under section 6 of the *Regulations*. Pharmascience again acknowledges that Teva could commence a patent infringement action in relation to Glatect 20 mg and the '437 Patent outside the *Regulations*, but there is no basis for a claim against Glatect 20 mg within the *Regulations* given that Pharmascience has already obtained its NOC. Pharmascience made extensive submissions on the interpretation of the *Regulations*.

[916] Although I share Pharmascience's overall view that the *Regulations* are a complete regime and once the NOC is issued, reliance on the *Regulations* should not be possible and, at its simplest, does not make sense, I need not decide this more complex jurisdictional issue in the present case.

[917] I have found that the '437 Patent is not valid and, therefore, Pharmascience will not infringe the '437 Patent by its Glatect 20 mg product in any event. Nor would Pharmascience infringe claim 16 of the '437 Patent with respect to its 40 mg product.

XXVII. Infringement by Pharmascience

[918] Pursuant to section 6 of the *Regulations*, Teva seeks a declaration that the making, constructing, using or selling of Pharmascience's Glatect 40 mg product in accordance with its SNDS would infringe the '437 and '802 Patents. As noted above, Pharmascience has already obtained a NOC for its Glatect 20 mg product.

[919] Teva submits that Pharmascience will directly or indirectly infringe or will induce infringement of the patents by the making, constructing, using or selling of glatiramer acetate 20 mg and 40 mg in accordance with Pharmascience's SNDS. Teva submits that Pharmascience's Glatect products are indicated for exactly the same patient population, in the same dosage strength and with the same dosage regimen to achieve the same outcomes.

[920] Pharmascience's arguments have been directed at the validity of the patents; if the patents are invalid, it will not infringe. Pharmascience also argues, with respect to the '437 Patent, that it would not infringe because its Glatect 40 mg product is not intended for the single attack patient but for patients who meet the criteria for a diagnosis of MS or RRMS.

[921] As noted above, as construed, the '437 Patent is directed at the CIS or single attack patient and not the patient who has already been diagnosed with MS pursuant to the McDonald criteria. The '437 Patent includes a 40 mg dosage.

[922] I have found that the '437 Patent is invalid due to obviousness, therefore, it will not be infringed by Pharmasciences's Glatect products.

[923] I have found that the '802 Patent is valid. I also find that Teva has met its burden to establish that, if Pharmascience's Glatect product is approved and marketed in accordance with Pharmascience's SNDS and proposed draft Product Monograph, Pharmascience will infringe, directly and indirectly, the '802 Patent because the Glatect 40 mg product is indicated for the same patient population, in the same dosage strength and with the same dosage regimen to achieve the same outcomes.

[924] The evidence of Drs. Morrow and Vosoughi clearly supports that physicians will prescribe, and patients will use, Glatect in a manner that infringes the asserted claims, as construed, of the '802 Patent and in the same manner as they would use Copaxone. Dr. Grant

confirmed that Glatect is the same as Copaxone. Pharmascience has not led any evidence to the contrary.

[925] In addition, Pharmascience will induce infringement, including through the use of the proposed combined Glatect Product Monograph, from which the Court can draw a reasonable inference (*Corlac Inc v Weatherford Canada Inc*, 2011 FCA 228 at para 162; *Janssen Inc v Apotex Inc*, 2019 FC 1355 at para 235).

[926] Pharmascience's regulatory expert, Ms. Picard, explained that a product monograph describes the properties, claims, indications and conditions of use of a drug product and contains other information related to ensuring the optimal, safe and effective use of the drug product. Ms. Picard noted that a product monograph is the up-to-date and highest level of the approved information by Health Canada and, once approved, would be publicly available.

[927] Pharmascience's expert, Dr. Green first stated that product monographs and labels were simply for patients and legal disclosure and were not relied on by physicians. However, he later agreed that he does consider product monographs.

[928] All the other experts agreed that that product monographs are used, along with other resources, to inform and guide the prescribing practices of physicians.

[929] Teva acknowledges that Pharmascience's Glatect 20 mg product is not affected by the outcome of this litigation because Pharmascience has already obtained a NOC for Glatect 20 mg.

However, the outcome of this litigation impacts the combined Glatect Product Monograph because Pharmascience seeks to replicate Copaxone's indications for its 40 mg product.

[930] Pharmascience's proposed combined Glatect Product Monograph for its 20 mg and 40 mg product provides its indications and mirrors the indications of Copaxone. Pharmascience has also acknowledged that its Glatect products will be used in accordance with its proposed combined Product Monograph.

[931] Pharmascience's proposed combined Glatect Product Monograph states:

> GLATECT (glatiramer acetate) is indicated for:
>
> <u>20 mg / mL once-daily</u>
>
> Treatment of ambulatory patients with Relapsing Remitting Multiple Sclerosis (RRMS), including patients who have experienced a single demyelinating event and have lesions typical of multiple sclerosis on brain MRI:
>
> - To decrease the frequency of clinical exacerbations
> - To reduce the number and volume of active brain lesions identified on MagneticResonance Imaging (MRI) scans
>
> <u>40 mg / mL three times per week</u>
>
> Treatment of ambulatory patients with Relapsing Remitting Multiple Sclerosis (RRMS):
>
> - To decrease the frequency of clinical exacerbations
> - To reduce the number and volume of active brain lesions identified on Magnetic Resonance Imaging (MRI) scans
>
> The safety and efficacy of GLATECT in chronic progressive MS have not been established.

[932] Teva's current Copaxone Product Monograph states:

> COPAXONE (glatiramer acetate) is indicated for:
>
> 20 mg/mL once-daily:
>
> Treatment of ambulatory patients with Relapsing Remitting Multiple Sclerosis (RRMS), including patients who have experienced a single demyelinating event and have lesions typical of multiple sclerosis on brain MRI:
>
> - To decrease the frequency of clinical exacerbations
> - To reduce the number and volume of active brain lesions identified on Magnetic Resonance Imaging (MRI) scans.
>
> 40 mg/mL three times-a-week:
>
> Treatment of ambulatory patients with Relapsing Remitting Multiple Sclerosis (RRMS):
>
> - To decrease the frequency of clinical exacerbations
> - To reduce the number and volume of active brain lesions identified on Magnetic Resonance Imaging (MRI) scans.
>
> The safety and efficacy of COPAXONE in chronic progressive MS have not been established.

[933] In conclusion, Pharmascience will infringe the ‘802 Patent if its SNDS is approved and it markets its Glatect products as described in the proposed Product Monograph.

XXVIII. Costs

[934] Although both parties raised the issue whether the Court should request submissions on costs from the parties before the issuance of this Judgment or within a reasonable period after Judgment, the Court omitted to make an order at the conclusion of the hearing.

[935] Given that the success of this Action is divided, I encourage the parties to consider whether an agreement can be reached with respect to costs. In the event that no agreement can be reached, the parties may provide cost submissions to the Court, not exceeding five pages, within 30 days of the issuance of this Judgment.

[936] In conclusion, I appreciated the comprehensive submissions and helpful compendia along with the flexibility exhibited by Counsel and the witnesses in the hearing of this Action.

JUDGMENT in files T-2182-18 and T-2183-18

THIS COURT'S JUDGMENT is that:

1. The Plaintiffs' infringement action (T-2182-18) against the Defendant with respect to Canadian Patent 2,702,437 is dismissed.

2. The Plaintiffs' infringement action (T-2183-18) against the Defendant with respect to Canadian Patent 2,760,802 (the "802 Patent") is granted.

3. The making, constructing, using or selling of glatiramer acetate 40 mg/1 mL prefilled syringes ("40 mg Glatect") by the Defendant in accordance with its Supplemental New Drug Submission filed on November 1, 2018 would infringe claims 1, 2, 3, 4, 22, 24, 25, 36-39, 47-57, 59, 60, and 63-66 of the 802 Patent, directly or indirectly or by the Defendant inducing infringement.

4. The Defendant and its subsidiary and affiliated companies, officers, directors, employees, agents, licensees, successors, assigns and any others over whom the Defendant exercises lawful authority, are enjoined from:

   a. making, constructing, using or selling 40 mg Glatect in Canada;

   b. offering for sale, marketing or having 40 mg Glatect marketed in Canada;

   c. importing, exporting, distributing or having 40 mg Glatect distributed in Canada; and

   d. otherwise infringing or inducing infringement of the 802 Patent.

5. In the event that the parties cannot reach an agreement on costs, the parties may make written submissions to the Court, not to exceed five pages, by January 28, 2021.

"Catherine M. Kane"

Judge

ANNEX 1

Claims of the 437 Patent

Claim 1

A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of glatiramer acetate for use in delaying the onset of clinically definite multiple sclerosis in a patient who experienced a single clinical attack suggestive of multiple sclerosis, who presents with at least one lesion consistent with multiple sclerosis and who is at risk of developing clinically definite multiple sclerosis and prior to development of clinically definite multiple sclerosis.

Claim 2

A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of glatiramer acetate for use in reducing progression of magnetic resonance imaging (MRI)-monitored disease activity in a patient who experienced a single clinical attack suggestive of multiple sclerosis, who presents with at least one lesion consistent with multiple sclerosis and who is at risk of developing clinically definite multiple sclerosis and prior to development of clinically definite multiple sclerosis.

Claim 3

A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of glatiramer acetate for use in reducing the progression of symptoms of Multiple Sclerosis in a patient who experienced a single clinical attack suggestive of multiple sclerosis, who presents with at least one lesion consistent with multiple sclerosis and who is at risk of developing clinically definite multiple sclerosis prior to development of clinically definite multiple sclerosis.

Claim 4

A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of glatiramer acetate for use in reducing the frequency of relapse in a patient who experienced a single clinical attack suggestive of multiple sclerosis, who presents with at least one lesion consistent with multiple sclerosis and who is at risk of developing clinically definite multiple sclerosis prior to development of clinically definite multiple sclerosis.

Claim 13

The pharmaceutical composition of any one of claims 1-12, wherein the use is once-a-day.

Claim 14

The pharmaceutical composition of any one of claims 1-13, wherein the use is subcutaneous.

Claim 15

The pharmaceutical composition of any one of claims 1-14, wherein the therapeutically effective amount of glatiramer acetate is 20mg.

Claim 16

The pharmaceutical composition of any one of claims 1-14, wherein the therapeutically effective amount of glatiramer acetate is 40mg.

Claim 19

The pharmaceutical composition of claim 3 wherein progression of symptoms is assessed by multiple sclerosis related disability in the patient as measured by Kurtzke Expanded Disability Status Scale (EDSS) Score, is assessed by relapse rate in the patient, or is assessed by the progression of MRI-monitored disease activity in the patient.

Claim 24

The pharmaceutical composition of claim 2 or 19 wherein the MRI-monitored disease activity is the mean number of new T2 lesions in the brain of the patient.

ANNEX 2

The 802 Patent – Claims at Issue

Claim 1

A medicament comprising glatiramer acetate for use in treating a human patient who is suffering from relapsing-remitting multiple sclerosis or who has experienced a first clinical episode and is at high risk of developing clinically definite multiple sclerosis, wherein the medicament is prepared for a regimen of three subcutaneous injections of a 40 mg dose of glatiramer acetate every seven days with at least one day between each subcutaneous injection.

Claim 2

Glatiramer acetate for use in a regimen of three subcutaneous injections of a 40mg dose of glatiramer acetate every seven days with at least one day between each subcutaneous injection to treat a human patient who is suffering from relapsing-remitting multiple sclerosis or who has experienced a first clinical episode and is at high risk of developing clinically definite multiple sclerosis.

Claim 3

A medicament comprising glatiramer acetate for use in treating a human patient who is suffering from relapsing-remitting multiple sclerosis or who has experienced a first clinical episode and is at high risk of developing clinically definite multiple sclerosis, wherein the medicament comprises a 40mg dose of glatiramer acetate and wherein the medicament is prepared for a regimen of three subcutaneous injections of a 40mg dose of glatiramer acetate every week with at least one day between each subcutaneous injection, and wherein the medicament is a pharmaceutical composition having a pH in the range of 5.5 to 8.5.

Claim 4

Glatiramer acetate for use in a regimen of three subcutaneous injections of a 40mg dose of glatiramer acetate every week with at least one day between each subcutaneous injection to treat a human patient who is suffering from relapsing-remitting multiple sclerosis or who has experienced a first clinical episode and is at high risk of developing clinically definite multiple sclerosis, and wherein the medicament is a pharmaceutical composition having a pH in the range of 5.5 to 8.5. 139.

Claim 22

The medicament of claim 1 or claim 3, or glatiramer acetate of claim 2 or claim 4, wherein the human patient is suffering from relapsing-remitting multiple sclerosis. 281.

Claim 24

The medicament of any one of claims 1, 3, 5 or 7, or glatiramer acetate of any one of claims 2, 4, 6 or 8 wherein the medicament is prepared as a pharmaceutical composition having a pH in the range of 5.5 to 7.0 or the glatiramer acetate is present in a pharmaceutical composition having a pH in the range of 5.5 to 7.0, wherein the pharmaceutical composition comprises 40 mg/ml glatiramer acetate and manitol.

Claim 25

The medicament of any one of claims 1, 3, 5, 9, 11, 13, 15, 17, 19 or 21-24 or glatiramer acetate of any one of claims 2, 4, 6, 10, 12, 14, 16, 18, 20-24, wherein during each week or each seven days the subcutaneous injections are on day 1, day 3 and day 5 of such week or seven days; day 1, day 3 and day 6 of such week or seven days; day 1, day 4 and day 6 of such week or seven days; day 2, day 4 and day 6 of such week or seven days; day 2, day 5 and day 7 of such week or seven days; or day 3, day 5 and day 7 of such week or seven days.

Claim 36

The medicament of any one of claims 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21-27, 29 or 31-35, or glatiramer acetate of any one of claims 2, 4, 6, 60 8, 10, 12, 14, 16, 18, 20-28, 30 or 31-35, wherein the regimen is effective for reducing the frequency of relapses in the human patient, reducing the mean cumulative number of Gd-enhancing lesions in the brain of the human patient, reducing the mean number of new T2 lesions in the brain of the human patient, reducing the cumulative number of enhancing lesions on T1-weighted images in the human patient, reducing brain atrophy in the human patient, increasing the time to a confirmed relapse in the human patient, reducing the total number of confirmed relapses in the human patient, reducing the progression of MRI-monitored disease activity in the human patient, reducing the total volume of T2 lesions in the human patient, reducing the number of new hypointense lesions on enhanced T1 scans in the human patient, reducing the total volume of hypointense lesions on enhanced T1 scans, reducing the level of disability as measured by EDSS Score in the human patient, reducing the change in EDSS Score in the human patient, reducing the change in Ambulation Index in the human patient, reducing the level of disability as measured by EuroQoL (EQ5D) questionnaire in the human patient, or reducing the level of disability as measured by the work productivity and activities impairment – General Health (WPAI-GH) questionnaire in the human patient.

Claim 37

The medicament of any one of claims 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21-27, 29 or 31-26, or glatiramer acetate of any one of claims 2, 4, 6, 8, 10, 12, 14, 16, 18, 20-28, 30 or 31-36, wherein the regimen is effective for reducing the frequency of relapses or exacerbations in the human patient.

Claim 38

The medicament of any one of claims 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21-27, 29 or 31-36, or glatiramer acetate of any one of claims 2, 4, 6, 8, 10, 12, 14, 16, 18, 20-28, 30 or 31-36, wherein the regimen is effective for reducing the frequency of relapses in the human patient.

Claim 39

The medicament or glatiramer acetate of claim 38, wherein the regimen is effective for further reducing the cumulative number of enhancing lesions on T1-weighted images of the human patient.

Claim 47

The medicament of any one of claims 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21-27, 29 or 31-46, or glatiramer acetate of any one of clams 2, 4, 6, 8, 10, 12, 14, 16, 18, 20-28, 30 or 31-46, wherein the regimen is effective for treating the human patient with or inducing reduced frequency and severity of immediate post injection reactions and injection site reactions in the human patient relative to administration of 20mg of glatiramer acetate s.c. daily.

Claim 48

The medicament of any one of claims 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21-27, 29 or 31-47, or glatiramer acetate of any one of claims 2, 4, 6, 8, 10, 12, 14, 16, 18, 20-28, 30 or 31-47, wherein the regimen is effective for alleviating a symptom of relapsing-remitting multiple sclerosis in the human patient.

Claim 49

A medicament comprising glatiramer acetate for use in reducing frequency of relapses or exacerbations in a human patient suffering from relapsing-remitting multiple sclerosis wherein the medicament is prepared for a regimen of three subcutaneous injections of a 40mg dose of glatiramer acetate every seven days with at least one day between each subcutaneous injection.

Claim 50

Glatiramer acetate for use in a regimen of three subcutaneous injections of a 40mg doses of glatiramer acetate every seven days with at least one day between each subcutaneous injection to reduce frequency of relapses or exacerbations in a human patient suffering from relapsing-remitting multiple sclerosis.

Claim 51

A medicament comprising glatiramer acetate for use in reducing the mean cumulative number of Gd-enhancing lesions in the brain of a 39 human patient, reducing the mean number of new T2 lesions in the brain of a human patient, reducing the cumulative number of enhancing lesions on T1-weighted images in a human patient, reducing the total volume of T2 lesions in a human

patient, reducing the number of a new hypointense lesions on enhanced T1 scans in a human patient or reducing the total volume of hypointense lesions on enhanced T1 scans in a human patient, wherein the human patient is suffering from relapsing-remitting multiple sclerosis, and wherein the medicament is prepared for a regimen of three subcutaneous injections of a 40mg dose of glatiramer acetate every seven days with at least one day between each subcutaneous injection.

Claim 52

Glatiramer acetate for use in a regimen of three subcutaneous injections of a 40mg dose of glatiramer acetate every seven days with at least one day between each subcutaneous injection to reduce the mean cumulative number of Gd-enhancing lesions in the brain of a human patient, reduce the mean number of new T2 lesions in the brain of a human patient, reduce the cumulative number of enhancing lesions on T1-weighed images in a human patient, reduce the total volume of T2 lesions in a human patient, reduce the number of new hypointense lesions on enhanced T1 scans in a human patient or reduce the total volume of hypointense lesions on enhanced T1 scans in a human patient, wherein the human patient is suffering from relapsing-remitting multiple sclerosis.

Claim 53

The medicament of any one of claims 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21-27, 29, 31-49 or 51, or glatiramer acetate of any one of claims 2, 4, 6, 8, 10, 12, 14, 16, 18, 20-28, 30, 31-48, 50 or 52, wherein the regimen is further effective for reducing the mean cumulative number of Gd-enhancing lesions in the brain of the human patient, reducing the mean number of new T2 lesions in the brain of the human patient or reducing the cumulative number of enhancing lesions on T1- weighted images in the human patient.

Claim 54

The medicament of any one of claims 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21-27, 29, 31-49, 51 or 53, or glatiramer acetate of any one of claims 2, 4, 6, 8, 10, 12, 14, 16, 18, 20-28, 30, 31-48, 50 or 52-53, wherein the regimen is effective for treating the human patient with or inducing reduced frequency of immediate post injection reactions or of injection site reactions in the human patient relative to administration of 20mg glatiramer acetate s.c. daily.

Claim 55

The medicament of any one of claims 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21-27, 29, 31-49, 51 or 53-54, or glatiramer acetate of any one of claims 2, 4, 6, 8, 10, 12, 14, 16, 18, 20-28, 30, 31-48, 50 or 52-54, wherein the regimen is effective for improving tolerability in the human patient relative to 20mg glatiramer acetate s.c. daily, wherein the increased tolerability comprises reduced frequency of immediate post injection reactions or reduced frequency of injection site reactions, each relative to the frequency experienced with 20 mg glatiramer acetate s.c. daily.

Claim 56

The medicament or glatiramer acetate, of any one of claims 47, 54 or 55, wherein the immediate post injection reaction is palpitations, feeling hot, flushing, hot flushes, tachycardia, dyspnoea, chest discomfort, chest pain, non-cardiac chest, asthenia, back pain, bacterial infection, chills, cyst, face edema, fever, flu syndrome, infection, injection site erythema, injection site hemorrhage, injection site induration, injection site inflammation, injection site mass, injection site pain, injection site pruritus, injection site urticaria, injection site welt, neck pain, pain, migraine, syncope, tachycardia, vasodilatation, anorexia, diarrhea, gastroenteritis, gastrointestinal disorder, nausea, vomiting, ecchymosis, peripheral edema, arthralgia, agitation, anxiety, confusion, foot drop, hypertonia, nervousness, nystagmus, speech disorder, tremor, vertigo, bronchitis, dyspnea, laryngismus, rhinitis, erythema, herpes simplex, pruritus, rash, skin nodule, sweating, urticaria, ear pain, eye disorder, dysmenorrheal, urinary urgency, or vaginal moniliasis.

Claim 57

The medicament or glatiramer acetate, of any one of claims 47, 54 or 55, wherein the injection site reaction is erythema, hemorrhage, induration, inflammation, mass, pain, pruritus, urticaria, or welt that occurs immediately around the site of injection.

Claim 59

The medicament of any one of claims 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21-27, 29, 31-49, 51 or 53-58, or glatiramer acetate of any one of claims 2, 4, 6, 8, 10, 12, 14, 16, 18, 20-28, 30, 31-48, 50 or 52-58, wherein the glatiramer acetate is present in 1ml of a pharmaceutical composition in a prefilled syringe for self administration.

Claim 60

Use of glatiramer acetate for the manufacture of a medicament for use in treating a human patient who is suffering from relapsing remitting multiple sclerosis or who has experienced a first clinical episode and is at high risk of developing clinically definite multiple sclerosis, wherein the medicament is prepared for a regimen of three subcutaneous injections of a 40mg dose of glatiramer acetate every seven days with at least one day between each subcutaneous injection.

Claim 63

Use of glatiramer acetate in the manufacture of a medicament for use in reducing frequency of relapses or exacerbations in a human patient suffering from relapsing-remitting multiple sclerosis wherein the medicament is prepared for a regimen of three subcutaneous injections of a 40mg dose of glatiramer acetate every seven days with at least one day between each subcutaneous injection.

Claim 64

Use of glatiramer acetate in the manufacture of a medicament for use in reducing the mean cumulative number of Gd-enhancing lesions in the brain of a human patient, reducing the mean number of new T2 lesions in the brain of a human patient, reducing the cumulative number of enhancing lesions on T1-weighted images in a human patient, reducing the total volume of T2 lesions in a human patient, reducing the number of new hypointense lesions on enhanced T1 scans in a human patient or reducing the total volume of hypointense lesions on enhanced T1 scans in a human patient, wherein the human patient is suffering from relapsing-remitting multiple sclerosis, and wherein the medicament is prepared for a regimen of three subcutaneous injections of a 40mg dose of glatiramer acetate every seven days with at least one day between each subcutaneous injection.

Claim 65

The use of any one of claims 60-64, wherein the medicament is a pharmaceutical composition comprising 40 mg/ml glatiramer acetate and mannitol, and having a pH in the range of 5.5 to 7.0. Claim 66.

The use of any one of claims 60-65, wherein the medicament is to be administered using a prefilled syringe by self administration.

FEDERAL COURT

SOLICITORS OF RECORD

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