**ASTEX THERAPEUTICS LIMITED vs ASTRAZENECA AB**

**2017. 6. 21 선고**

Introduction

1. Alzheimer's Disease ("AD") is a major health issue. At present, there is no cure or treatment for the condition. Since the early 1990s, it has been hypothesised that the development of the amyloid-ß ("Aß") plaques in the brain associated with AD is connected with the breakdown of amyloid precursor protein ("APP") caused by cleaving enzymes including ß-secretase or **BACE (Beta-site Amyloid precursor protein Cleaving Enzyme)**. Accordingly, the development of a BACE inhibitor has long been a goal of many companies in the pharmaceutical industry.
2. The Defendant ("AstraZeneca") was at all material times, and remains, a substantial pharmaceutical company. At the relevant times, the Claimant ("Astex") was a small drug discovery company which was reliant upon collaborations with larger pharmaceutical companies, although it became part of the large Otsuka Group in October 2013.
3. In 1999 AstraZeneca commenced a BACE inhibitor project at its site in Wilmington in the USA. In 2002 Astex also started work on developing a BACE inhibitor. On 21 February 2003 the parties entered into a **Research Collaboration and License Agreement** ("the Agreement") to collaborate on the development of a BACE inhibitor. The Agreement provided among other things for a collaborative research project which after a Collaboration Term could be continued by AstraZeneca alone; for certain milestone payments to be made by AstraZeneca to Astex in certain circumstances; for AstraZeneca to own any selected Candidate Drug and any associated intellectual property rights; and for Astex to receive a royalty on sales of any Licensed Product which contained a Collaboration Compound as defined in Section 1.7 of the Agreement.
4. **The Collaboration Term lasted from 21 February 2003 until 20 April 2005**. Thereafter AstraZeneca continued the project on its own, primarily at its site in Södertälje in Sweden. Some years later, two compounds referred to internally by AstraZeneca as AZD3839 and AZD3293, and referred to in these proceedings as CD1 and CD2, were developed. Both CD1 and CD2 were nominated by AstraZeneca as Candidate Drugs under the Agreement and milestone payments were made by AstraZeneca to Astex in respect of CD1. CD1 progressed to Phase I clinical trials, but subsequently its development has been discontinued. The structures of CD1 and CD2 are shown below, with three of the rings marked A, B and C for identification.



1. In September 2014 AstraZeneca announced that it had entered into an agreement with Eli Lilly ("Lilly") under which Lilly was to conduct a large scale Phase II /III clinical trial of CD2. CD2 is currently in the Phase III arm of that trial. On 24 February 2015 AstraZeneca informed Astex that it had reviewed the position and now considered that neither CD1 nor CD2 were Collaboration Compounds within the Agreement. That led to this action.
2. The principal issues are as follows:

i) is CD1 a Collaboration Compound?

ii) is CD2 a Collaboration Compound?

iii) if CD1 is not a Collaboration Compound, is AstraZeneca entitled to recover the milestone payments it paid in respect of CD1?

iv) is the Agreement capable of expiring?

1. The resolution of these issues depends in part on the interpretation of the Agreement and in part on the factual questions of precisely how CD1 and CD2 were developed. Although Astex relies upon AstraZeneca's statements and conduct both at the time of, and subsequent to, the development of CD1 and CD2, as shedding light on the answers to the factual questions, it is common ground that such statements and conduct are inadmissible as aids to construction of the Agreement. Furthermore, Astex does not contend that AstraZeneca is estopped by those statements or conduct.

The Agreement

1. The Agreement is a lengthy, detailed and complex agreement running to 67 pages (albeit double-spaced). It has the appearance of being professionally drafted, in the sense of being drafted by a person or persons with legal expertise. Although neither party is American, the language of the Agreement mainly (although not entirely) has American spellings. Although the Agreement must be interpreted as a whole, I obviously cannot set it all out. I shall, however, set out the principal provisions which are relevant to the issues. I shall adopt the terminology used in the Agreement of referring to its provisions as "Sections".
2. The Agreement begins with five recitals, of which the first and fourth are as follows:

"WHEREAS, ASTRAZENECA currently performs an internal project aiming at the discovery and development of novel therapeutic pharmaceutical products active at the Target (as defined below) for treatment of Alzheimer's disease or senile dementia (the 'Project'); and

…

WHEREAS, the Parties wish to engage in a collaborative research program under the Project utilising ASTEX's proprietary Pyramid™ technology for discovery of novel chemical leads active against the Target and suitable for development for treatment of Alzheimer's disease or senile dementia (the 'Program')."

1. Section 1 of the Agreement contains a long series of definitions, including the following:

"1.2 'Affinity Hit' or 'AFFIT' means any Material that shows specific binding to the Target in the screens performed under the Program, meeting the criteria set forth in the Research Plan provided, however, that if any such Material is later selected as a Hit it ceases to be an AFFIT and shall for all purposes thereafter be regarded only as a Hit.

…

1.4 'AFFIT Optimisation' means chemical structure modification performed as part of the Program, starting from AFFITs and aiming to generate optimised AFFIT structures ('AFFIT Improvements') that, together with AFFITs, form the bases for identification of Hits.

…

1.6 'Candidate Drug' or 'CD' means a Collaboration Compound satisfying ASTRAZENECA's pharmacological and pharmaceutical criteria for clinical testing, as outlined in the Research Plan, and which compound has been selected for clinical testing by the JEC or ASTRAZENECA.

1.7 'Collaboration Compound' means all Hits, Lead Compounds, CDs and other substances and structures discovered or identified as a direct result of AFFIT Optimisation, Hit Optimisation or Lead Optimisation and any metabolites, prodrugs, isomers and enantiomers referable to any of the foregoing. In the event of a dispute between the Parties as to whether or not a given substance or structure was discovered as a direct result of Hit Optimisation or Lead Optimisation the Parties' internal laboratory books and records from the relevant process through which such substance or structure was discovered shall serve as exclusive evidence to resolve any such dispute. For the avoidance of doubt, AFFITs and AFFIT Improvements do not constitute Collaboration Compounds (but constitute Results).

…

1.9 'Collaboration Term' means the term during which ASTEX performs research activities under the Program as specified in Section 14.2 below

…

1.14 ''Effective Date' means the date first written above in this Agreement.

…

1.17 'Hits' means all AFFITs and AFFIT Improvements selected by the JEC or by ASTRAZENECA as candidates for Hit Optimisation.

1.18 'Hit Optimisation' means chemical structure modification performed as part of the Program, starting from a Hit and aiming at the identification of compounds with properties meeting the Lead criteria (as defined in the Research Plan).

…

1.22 'JEC' means the Joint Executive Committee established by the Parties pursuant to Section 3 below.

1.23 '**Lead Compounds**' or 'Leads' means all Hits and all other substances and structures discovered or identified through Hit Optimisation meeting the Lead criteria (as defined in the Research Plan) of the Program, which have been selected by the JEC or, **after the Collaboration Term**, by ASTRAZENECA as candidates for Lead Optimisation.

1.24 '**Lead Optimisation**' means chemical structure modification performed as part of the Program, starting from a Lead Compound and aiming at the identification of compounds with properties meeting the CD criteria (as outlined in the Research Plan, which outline may subsequently be amended by ASTRAZENECA at its sole discretion).

1.25 'Licensed Product' means a pharmaceutical product containing one or more Collaboration Compounds for which the first application for Royalty-bearing Collaboration Patent was made anywhere in the world within ten (10) years from the Effective Date …

1.26 'Materials' means any compounds (and fragments thereof) included in the Screening Libraries, and any other materials … that are used by a Party or the Parties in the Program, excluding any Collaboration Compounds and other Results.

….

1.32 '**Program**' means the research program described in the Research Plan, to be performed in collaboration by the Parties during the Collaboration Term as part of the Project, which thereafter may be continued by or on behalf of ASTRAZENECA alone.*"*

…

1.35 '**Project**' means the ASTRAZENECA project referenced in the first whereas clause of this Agreement.

…

1.37 'Research Plan' means the document attached hereto as Schedule 1.37 outlining the Program and each Party's undertakings and obligations in relation thereto. It is acknowledged that upon execution of this Agreement, some of the undertakings have only been possible to broadly outline in the Research Plan, the details of which shall be determined in good faith by the Parties through the JEC for each stage of the Program pursuant to Section 3.1 below.

1.38 '**Results**' means any ideas, inventions, discoveries, know-how, data, documentation, writings, designs, computer software, processes, principles, methods, techniques and other information, recorded in any form that is discovered, conceived, reduced to practice or otherwise generated through work performed under the Program during the Collaboration Term by either ASTEX or ASTRAZENECA or by the Parties jointly, but excluding Technology Results.

…

1.42 'Target' means any and all of beta secretase (BACE) … and any mutants, fragments and polymorphic forms of any of the foregoing.

1.43 '**Technology Result**' means any ideas, inventions, discoveries, know-how, data, documentation, writing, designs, computer software, processes, principles, methods, techniques and other information recorded in any form that is discovered, conceived, reduced to practice or otherwise generated through work performed under the Program by either ASTEX or ASTRAZENECA or by the Parties jointly and that constitutes a research method or research tool that is widely and generically applicable outside the scope of the Program and not specifically related to the Target or any Collaboration Compound and that does not constitute an Improvement to either Party's Background Technologies. …"

1. Section 2 of the Agreement includes the following provisions:

"2.1 During the term of this Agreement, each Party shall cooperate with the other and perform its obligations under this Agreement in good faith and in a commercially reasonable and workmanlike manner. Following the Effective Date, the Parties shall promptly commence the Program.

…

2.5 Materials that have become AFFITs, including any intellectual property rights related thereto, shall form part of the Results …

2.9 Subject to any license granted to ASTEX pursuant to Section 5.3, the Parties acknowledge and agree that ASTRAZENECA shall have the right in its sole discretion at any time during or after the Collaboration Term, irrespective of whether any Collaboration Compound(s) have already been selected for further optimisation or as CDs and whether or not any such compound(s) have failed in research, clinical development or on the market, to select additional AFFITs, AFFIT Improvements and Collaboration Compounds for optimisation and/or clinical development. ASTRAZENECA shall without delay notify the JEC of any such selections or, if such selections are made after the Collaboration Term, ASTRAZENECA shall similarly notify ASTEX."

1. **Section 3 of the Agreement deals with the management of the Program**. It provides for the establishment of the JEC, consisting of six members with equal numbers appointed by each party. Section 3.1 provides that the JEC will "oversee the operational responsibilities for the initiation, planning and performance of the activities under the Program."
2. Section 3.1 goes on to provide that the JEC's activities shall include, among other things:

"Determining within thirty (30) days of the completion of each stage of the Program the successful completion of such stage and deciding whether or not to continue the Program into the next stage (i.e. making "stop/go decisions"), provided that should the JEC decide not to proceed with the Program into the next stage, ASTRAZENECA shall be deemed to have terminated the Agreement pursuant to Section 14.3 below.

…

Determining if and when the Program Milestones have been met and the date of expiration of the Collaboration Term; and

Upon expiration or termination of the Collaboration Term, list[ing] by category all AFFITs, Hits, Leads and CDs generated up to the date of such expiration or termination in a document to be enclosed to this Agreement as Schedule 3.1."

1. Section 3.3 provides for the JEC to endeavour to reach consensus decisions, with disagreements to be resolved by the senior management of the parties. If disagreements cannot be resolved, AstraZeneca has the final say "other than with regards to disputes over whether payment is due ASTEX under this Agreement".
2. Sections 3.6, 3.7 and 3.8 provide, so far as relevant, as follows:

"3.6 The JEC shall keep accurate minutes of its deliberations, which minutes shall record all decisions and all actions recommended or taken, Program progress reports, Results generated of any significance to the Program and confirmation that Program Milestones have been reached. In particular, all AFFITS, Hits, Lead Compounds and CDs nominated during the Collaboration Term shall be recorded in the minutes of the JEC. …

3.7 Following the expiration of the Collaboration Term the JEC shall be dissolved and ASTEX shall provide ASTRAZENECA with consultation services as ASTRAZENECA may reasonably request for the continuation of the Project. ASTRAZENECA shall reimburse ASTEX for out of pocket costs incurred in connection with such consultations services. If the consultation services provided by ASTEX should exceed one (1) FTE day in any calendar year, ASTRAZENECA will compensate ASTEX for any additional FTE days at ASTEX's then applicable FTE rate. ...

3.8 Upon dissolution of the JEC pursuant to Section 3.7 above, ASTRAZENECA will provide ASTEX with Project reports every six months, updating Project progress and future plans. Each Party shall nominate one point of contact for all post-Program contacts between the Parties."

1. Section 4 of the Agreement deals with Reports. Section 4.1 provides, so far as relevant:

"No later than five (5) business days prior to each quarterly JEC meeting, each Party shall provide the JEC with a detailed written progress report in English containing, without limitation, specifications and other information on all Results generated of any significance to the Program and not previously reported to the JEC. …"

1. **Section 5 of the Agreement deals with ownership of the Results, and the grant of rights by the parties to each other, in considerable detail**. Section 5.1 provides that the parties jointly own all Results and Technology Results. This is subject to two exceptions: first, upon selection of any CD, AstraZeneca exclusively owns all Results specifically relating to that CD; and secondly, each party exclusively owns all Results that constitute Improvements to that party's Background Technologies. By Section 5.2 Astex grants AstraZeneca a worldwide perpetual licence, which is exclusive during the term of the Agreement, under Astex's rights to the Results jointly owned by the parties, including for research and development of pharmaceutical products. By Section 5.3 each party grants the other a perpetual, non-exclusive, worldwide, royalty-free licence to use and exploit all AFFITs, AFFIT Improvements and Technology Results for Program-Independent Activities. By Section 5.5 AstraZeneca undertakes to use Commercially Reasonable Efforts to clinically develop at least one CD with the time to bring such CD to the market as a Licensed Product, but Section 5.5.1 permits AstraZeneca to put clinical development of a CD on hold for up to 18 months. If AstraZeneca puts clinical development of a CD on hold for longer, then Section 5.5.2 permits Astex to demand an exclusive worldwide licence to clinically develop and exploit such CD.
2. **Section 6 deals with the funding of the research**, and in particular Section 6.1 provides for AstraZeneca to fund Astex's work on the Program at specified rates during the Collaboration Term capped at US$1,050,000.
3. Section 7 of the Agreement includes the following provisions:

"**7.1 The milestone and royalty payments** outlined below, taken together with the funding to be provided pursuant to Section 6 above, shall be all-inclusive and ASTEX shall not be entitled to any additional compensation or remuneration from ASTRAZENECA under the Agreement unless and to the extent separately agreed by the parties in writing. …

7.2. Within thirty (30) days of the determination by JEC or ASTRAZENECA, as applicable, that the respective Program Milestone identified below and has occurred, ASTRAZENECA will make the following payments to ASTEX:

1) Program Milestone 1: two hundred fifty thousand (250,000) $US following identification of the first Hit.

2) Program Milestone 2: seven hundred fifty thousand (750,000) $US following identification of the first chemical series out of two required to meet the HI to LI transition criteria as set out in Section 3.2 of the Research Plan; and

3) Program Milestone 3: one million (1,000,000) $US following first nomination of a Collaboration Compound as a CD pursuant to Section 3.6 of the Research Plan;

7.3. Within 30 days of the occurrence of the respective event specified below (each a 'Development Milestone') ASTRAZENECA will make the following payments to ASTEX:

1) One million (1,000,000) $US following the first IND approval of a Collaboration Compound obtained by or on behalf of ASTRAZENECA;

2) Two million (2,000,000) $US following the initiation by or on behalf of ASTRAZENECA of the first phase II clinical trial on a Collaboration Compound …;

3) Five million (5,000,000) $US following the initiation by or on behalf of ASTRAZENECA of the first phase III clinical trial on a Collaboration Compound …;

…

7.4 Each of the payments in relation to the Program Milestones set forth under Section 7.2 and Development Milestones under Section 7.3 will be made no more than once under the Agreement …"

1. **Section 8 of the Agreement deals with the payment of royalties by AstraZeneca to Astex in respect of Net Sales of Licensed Products**. Sections 9, 10 and 11 deal with publication, confidentiality, and patent prosecution and defence respectively. The confidentiality obligation contained in Section 10.1 is expressed to last "for a period of five (5) years after termination or expiration of this Agreement". Section 12 deals with representations and warranties, and section 13 indemnification and insurance.
2. Section 14 of the Agreement includes the following provisions:

"14.1 This Agreement shall become effective upon the Effective Date and shall continue in full force and effect, unless earlier terminated in accordance with this Section 14, during the Collaboration Term and thereafter for as long as ASTRAZENECA is pursuing pre-clinical research referable to the Results and/or clinical development of one or more Collaboration Compounds and/or commercialising Licensed Product to which royalties are owed to ASTEX pursuant to Section 8 of this Agreement.

14.2 **The Collaboration Term shall commence on the Effective Date and continue for as long as ASTEX performs research activities under the Program. As set forth under Section 3.1, the JEC shall determine the date of expiration of the Collaboration Term**.

14.3 If ASTRAZENECA determines, in its sole discretion, that it is no longer desirable or feasible for it to pursue the Program up to selection of CD(s) or thereafter to clinically develop CD(s) or to sell Licensed Products for any reason including, without limitation, scientific, safety, technical, regulatory and commercial reasons, ASTRAZENECA may at any time terminate this Agreement in its entirety by giving ASTEX written notice to that effect. …

14.4 Notwithstanding Section 14.3 and 21.1, and without prejudice to any other remedies available by law or in equity, the Parties hereby renounce their respective right to terminate this Agreement for breach. ….

14.5 Either party may, in addition to any other remedies available to it by law or in equity, terminate this Agreement by written notice to the other party in the event (i) the other party shall have become insolvent or bankrupt, or shall have made an assignment for the benefit of its creditors, or (ii) there shall have been appointed a trustee or receiver of the other party or for all or a substantial part of its property, or (iii) any case or proceeding shall have been commenced or some other action taken by or against the other party in bankruptcy ….

14.6 Should ASTEX undergo a **Change of Control** (as defined below) ASTRAZENECA shall be entitled at its sole discretion and with immediate effect to either (i) terminate the Parties' collaboration on the Program or (ii) to terminate this Agreement in its entirety. …

14.6.1 In the event ASTRAZENECA elects to terminate the Parties' collaboration on the Program pursuant to Section 14.6 (i), and thereby to end the Collaboration Term, ASTRAZENECA shall be under no obligation to provide ASTEX with any further information on Results generated and any Program or Project progress reports provided to ASTEX will be limited to information as to whether the Program and/or Development Milestones have been met. …

…

14.9 The respective rights and obligations of the Parties under Sections 2.4, 2.5, 4.2, 5.1-5.5, 9.1-9.3, 10.1-10.3, 11.1-11.4, 12.1-12.5, 13.1-13.4, **14.3**, 14.6-14.9, 15 and 16 shall, unless otherwise specifically stated therein, **survive the termination or expiration of this Agreement**."

1. Sections 15 to 21 deal with various legal matters and formalities, including provision for the Agreement to be interpreted in accordance with the laws of England and for the parties to submit to the exclusive jurisdiction of the English courts.
2. Schedule 1.37 sets out the Research Plan. Part 1 states:

"This document outlines the Program and specifies the activities undertaken by ASTRAZENECA ('AstraZeneca') and ASTEX ('Astex') respectively in their mutual quest to discover a novel, potent and selective ß-secretase inhibitor that is suitable for developing into an orally active drug for Alzheimer's disease ('AD'). The Program, outlines projected resources, timelines and screening cascade to successfully achieve sequential Program transitions from AFFIT Identification (AI) to Hit generation ('HI'), to Lead identification ('LI'), to Lead optimization ('LO') and finally to nomination of one or more CDs.

The plan calls for stage wise delivery of the following:

• '**AFFITs**', 'AFFITs', are essentially weak ligands identified by physical methods that can determine specific interactions between the ligands and a target protein. Affinity NMR analysis is one example. The use of X-ray affinity analysis to determine specific binders (specific binding defined as <1 µM affinity with sufficient electron density in the active site) allows a binding mode to be determined with a high degree of certainty.

• **Improved AFFIT**, which are optimized AFFITs demonstrating BACE inhibitory activity (in enzymological assays), with specific binding properties and with an affinity in the <100 µM range.

• **Hits**, which are selected from the AFFITs and Improved AFFIT and will then progress to 'validated hits', and enable the Program to enter into the LI phase. In general, a Hit will be a pure compound with known structure, a potent inhibitor of BACE activity (< 10 µM) that possesses demonstrable SAR with significant degree of selectivity against other aspartyl protease (> 10 fold), and without undesirable chemical functionality from a CNS drug development point of view.

• **Leads and CDs** which have the properties described in Table 3.1 below."

1. It is common ground that the reference to "<1 µM" in the paragraph describing AFFITs is a typographical error and should read <1 mM.
2. Part 2 sets out the anticipated timeline for Program activities reproduced below.



1. It then states:

"As used in this Research Plan 'MS1' through 'MS4' refers to the generic discovery milestones defined and used within the AstraZeneca Global Discovery organization. When the success criteria for a stage of the Program has been met the Program may, subject to JEC decision pursuant Section 3 of the Agreement, transition into the following stage of the Program as set forth herein. Such transition does not necessarily mean that the stage for which the success criteria have been met is completed since JEC may decide to continue such stage to generate further results."

1. Part 3 begins with the following statement:

"The following table outlines key activities to be undertaken at each stage and the criteria to be achieved for successful transition to the next stage. These activities and the transition criteria cascade from the overall goal of delivering a ß-secretase inhibitor with desired CD profile. … "

1. The table sets out key activities under the following headings and success criteria are introduced with the following statements:

"**3.1. AFFIT Identification (Al) and Hit Identification (HI)**

…

**3.2 Hit Identification (HI)**

Success criteria for completion of HI: Once at least two distinct chemical series have been identified meeting criteria outlined below, the Program may enter LI, which the parties anticipate by end of 2003.

….

**Success criteria for completion of HI**

…

Potency in vitro better than 10 µM

…

Compounds are patentable

**3.3 Lead Identification (LI)**

…

Success criteria for completion of LI: Once at least two distinct chemical series have been identified meeting the criteria outlined below, the Program enters LO. The parties anticipate that to happen by end of 2004 and that the LO will go on for approximately 2 years before the LO success criteria are met.

…

**Success criteria for completion of LI**

…

Structural novelty for patenting

…

*In vitro* potency < 100 nM

…

DMPK profile in *vitro* and *in vivo* amenable to achieving CDTP [setting out details of metabolic stability, permeability and CNS penetration]

…

Endorsement by AZ

**3.4 Lead Optimization (LO)**

…

Success Criteria for completion of LO: Once sufficient number of compounds to be decided by JEC has been selected meeting the criteria outlined below, the Program enters the pre-CD nomination stage. The parties anticipate that to happen by end of 2006.

**3.5 Pre-CD nomination stage ('pre-nomination')**

The following are 'generic' criteria for project transition from LO to the CD pre-nomination stage. Specific criteria applicable to the Program will be established during early LO stage.

…

AstraZeneca may amend the pre-nomination criteria from time to time at its sole discretion.

Success criteria for completion of Pre-CD nomination stage: Following nomination of one or more compounds meeting the criteria outlined below, CD(s) may be nominated. The parties anticipate that to happen by end of 2007.

**3.6 CD Nomination and initiation of concept testing MS5**

The following are 'generic' criteria for CD nomination. Specific criteria applicable to the Program will be established by AstraZeneca during the LO stage.

…

AstraZeneca may amend the CD criteria from time to time at its sole discretion."

1. Paragraphs 3.1, 3.3 and 3.4 (but not paragraphs 3.2, 3.5 or 3.6) identify certain activities to be undertaken by Astex and AstraZeneca respectively. It can be seen from paragraph 3.4 of the table that it was envisaged that Astex would provide "structural crystallography support" "[f]or duration of LO".
2. Appendix 3 to the Research Plan sets out a draft Candidate Drug Target Profile (CDTP) and states that a specific CDTP applicable to the Program will be established by AstraZeneca during LO stage.

The 2009 Agreement

1. On 21 and 28 April 2010 Astex and AstraZeneca executed a further agreement dated and expressed to be effective of 1 August 2009 ("the 2009 Agreement"). The 2009 Agreement amended the Agreement in certain minor respects. More importantly, for present purposes, clause 2.3 provided, among other things:

"The Parties confirm that:

a. **The Collaboration Term expired on April 20, 2005**.

b. The list by category of all AFFITs, Hits, leads and CDs generated up to the end of the Collaboration Terms referred to in Article 3.1 of the Agreement (Schedule 3.1) has been prepared and agreed by the Parties and is enclosed to this Amendment."

1. The list of compounds attached to the 2009 Agreement runs to 127 pages and contains about 1355 compounds. Contrary to what is stated in the 2009 Agreement, the list does not categorise these compounds into AFFITs, Hits, Leads or CDs.

The factual witnesses

1. Although Section 1.7 of the Agreement provides that, in the event of a dispute as to whether or not a substance was discovered as a direct result of Hit Optimisation or Lead Optimisation, the parties' internal laboratory books and records from the relevant process through which such substance was discovered "shall serve as exclusive evidence to resolve any such dispute", it is common ground that this is not to be understood as excluding testimony from witnesses. Accordingly, I heard evidence from a considerable number of witnesses. It should be noted that many of the witnesses are no longer employed by either party, and thus were independent witnesses. All of the witnesses were good witnesses, although some had better recollections than others. There were few conflicts of evidence between the witnesses, as opposed to unsurprising differences of recollection, perspective, emphasis and interpretation. Counsel for Astex nevertheless reminded me that a witness may be perfectly sincere in their evidence, but mistaken in their recollection, relying in particular upon the observations of Leggatt J in *Gestmin SGPS SA v Credit Suisse (UK) Ltd* [[2013] EWHC 3560 (Comm)](http://www.bailii.org/ew/cases/EWHC/Comm/2013/3560.html%22%20%5Co%20%22Link%20to%20BAILII%20version) at [15]-[21]. Not only do I accept that, but also it seems to me that Section 1.7 reinforces the need which I would in any event feel, given that many of the key events in question occurred between 10 and 15 years ago, to place considerable weight on the documentary evidence.

*Astex's witnesses*

1. Astex called two factual witnesses:

i) **Dr Christopher Murray** obtained a BA in Chemistry from the University of Cambridge in 1986 and a PhD in Quantum Chemistry from the same institution in 1989. Between 1982 and 1992 he held two post-doctoral positions in Quantum Chemistry. From 1992 to 2000 he worked as a computational chemist for Protherics Molecular Design. Since November 2000 he had been employed by Astex successively as Head of Computational Chemistry, Director of Computational Chemistry and Informatics, Vice President of Computational Chemistry and Informatics, Vice President of Discovery Technology and Senior Vice President of Discovery Technology Team and is a member of its executive management. He has over 80 scientific publications and 40 patent applications to his name. **Dr Murray led Astex's BACE team from July 2002 until after the end of the Collaboration Term**. He was a fair and balanced witness in his oral evidence, but I consider that parts of his witness statements were somewhat tendentious and based on hindsight.

ii) **Dr Christof Angst** obtained a PhD in Chemistry from ETH Zurich in 1981. He held post-doctoral positions at Yale University from 1981-82 and at Stanford University School of Medicine from 1988-89. From August 1997 to August 2011 he was employed by AstraZeneca successively as: (i) Vice President, CNS Discovery, Wilmington (to December 2004); (ii) Vice President, Portfolio Enhancement (January 2005 to July 2010); and (iii) Vice President, Strategy CNS and Pain innovative Medicines ("iMed"). From January 2004 to July 2010, Dr Angst was a member of the Research Area Management Team ("RAMT") for the CNS and Pain area, which was responsible for overseeing the MS3 (until 2005), MS4 and MS5 transitions, and headed the Lead Generation Team ("LGT", also known as the Lead Generation Committee or "LGC"), which was responsible for the MS3 (from 2005) and MS2 (from 2008) transitions. **He also was part of the AstraZeneca team which negotiated the Agreement with Astex**. In the second role, he oversaw the BACE project and recommended the payment of milestone payments to Astex. In the third role, he recommended the payment of the milestone payment following the selection of CD1. Since retiring from AstraZeneca, he has acted as a consultant in the pharmaceutical and biotechnology industry. Counsel for AstraZeneca submitted that Dr Angst's evidence manifested an understandable desire to justify the view he had taken at the time that CD1 was a Collaboration Compound. I think there is some force in this. More importantly, it is clear that, equally understandably, **Dr Angst did not have a detailed knowledge of what had actually been done at Södertälje after the BACE project was transferred from Wilmington**. This is illustrated by his evidence that a plan had been made to modify the DHIZ core in order to lower the pKa at the computational chemistry workshop in September 2005. Dr Kolmodin convincingly explained that Dr Angst's evidence was inaccurate in this respect.

*AstraZeneca's witnesses*

1. AstraZeneca called the following witnesses in the following order:

i) **Dr Philip Edwards** obtained a BA in Chemistry from Rutgers University at Camden in 1978 and a PhD in Synthetic Organic Chemistry from the University of Colorado at Boulder in 1982. He held a National Institutes of Health post-doctoral fellowship at the later institution from 1982 to 1984. He was employed by AstraZeneca as a Medicinal Chemistry Team Leader at Wilmington from 1984 to 2008, apart from a secondment to AstraZeneca's Macclesfield site from 1990 to 1992. **Dr Edwards was the Lead Chemist on the BACE project at Wilmington from May 2000 to May 2005 and from October 2005 to July 2006**. He was a Medicinal Chemistry Consultant to AstraZeneca from 2008 to 2010. Since then he has been fully retired. Despite that, he had a reasonably good recollection of the events in question.

ii) **Mr Stefan Berg** obtained a Master's degree in Organic Chemistry from Stockholm University in 1988. From January 1988 to March 2013 he was employed by AstraZeneca successively as an organic chemist, as Chemistry Project Leader, Project Leader, Team Leader, Principal Scientist and Associate Director. **He was Lead Chemist and Project Leader on AstraZeneca's BACE project after it was moved from Wilmington to Södertälje**. Since leaving AstraZeneca, Mr Berg has been Chief Executive Officer of Berg Life Science Consulting, a consultancy company. As Mr Berg accepted, he did not have much recollection of the events in question independent of the documents.

iii) **Dr Stefan von Berg** obtained a degree in chemistry from RWTH Aachen University in 1995 and a doctorate in synthetic organic chemistry from the same institution in 1998. From 1998 to 2001 he undertook post-doctoral research at the Scripps Research Institute. He has been employed by AstraZeneca since March 2001, initially as Senior Research Scientist and more recently as Associate Principal Scientist. He was acting Chemistry Team Leader on the BACE project in Södertälje from September 2007 until at least December 2009.

iv) **Dr Karin Kolmodin** obtained an MSc in Molecular Biotechnology from Uppsala University in 1996 and a PhD in the same subject from the same institution in 2001. From November 2001 to 2012 she was employed as a Senior Research Scientist by AstraZeneca. From November 2001 to April 2004 she worked as a computational chemist at AstraZeneca's Structural Chemistry Laboratory ("SCL") in Mölndal in Sweden, after which she moved to the Södertälje site. After a period as a Principal Scientist at Sprint Bioscience, she has been employed for some time as a Team Coordinator by the Swedish Pensions Agency in its data department. Despite that, she had an impressive grasp of the chemistry with which she had been involved.

v) **Dr Sofia Karlström** obtained a Master's degree in Organic Chemistry from Uppsala University in 1995 and a PhD from Stockholm University in 2000. From 2000 to 2001 she undertook post-doctoral work at the Universidad de Alicante. From January 2002 to December 2012 she was employed by AstraZeneca successively as Senior Research Scientist, Chemistry Project Leader, Team Leader and Associate Principal Scientist. She joined the BACE project at Södertälje in mid-2005 as Chemistry Project Leader from 2006 and Team Leader from June 2007 to 2010. Since January 2013 she has been employed by Medivir, initially as Principal Scientist and more recently Director of Medicinal Chemistry. Much of her evidence was not challenged in cross-examination.

vi) **Mr Tobias Ginman** obtained an MSc in Chemical Engineering from KTH Royal Institute of Technology in 2000. From September 2000 to March 2006 he was employed as a research scientist by Biovitrum. From March 2006 to April 2012 he was employed by AstraZeneca, initially as a Research Scientist and latterly as a Senior Research Scientist. From spring 2008 to April 2012 he worked on the BACE Lead Generation program at Södertälje, from May 2010 as Head of Synthesis and from December 2011 as Head of Design. Since May 2012 he has been employed by Sprint Bioscience, where he is currently an Associate Principal Scientist and Laboratory Manager. Mr Ginman quoted from a published paper in his first witness statement, but the passage he quoted was in fact taken from an earlier draft which had been omitted from the published version. This was a minor and isolated lapse in the care with which the evidence had been prepared, however.

vii) **Dr Laszlo Rakos** obtained a Master's degree in Chemistry and Chemical Engineering from the Royal Institute of Technology in 1985 and a PhD in Organic Chemistry from the same institution in 1991. From 1992 to 2004 he held positions as a research scientist at a number of companies. From June 2004 to 2012 he was employed by AstraZeneca as a Senior Research Scientist at Södertälje, from December 2005 as synthetic chemist in the Lead Identification team. From January 2014 to June 2015 he worked as a teacher and since August 2015 he has been studying pedagogics at the University of Linne.

viii) **Dr Samantha Budd Haeberlein**, who I will refer to as "Dr Budd" to avoid confusion with her husband Dr Marcus Haeberlein, who also worked for AstraZeneca and features briefly in the story, obtained a BSc in Biochemistry from the University of Dundee in 1994 and a PhD in the same subject from the same institution in 1997. From 1997 to 1999 she was a post-doctoral researcher and then Instructor at Boston Children's Hospital and then Brigham & Women's Hospital, both at Harvard Medical School. From 1999 to 2000 she was Assistant Professor at the Centre for Neuroscience Research at the Burnham Institute in San Diego. She was employed by AstraZeneca from 2000 to January 2015 successively as Discovery Scientist, as Director and Neurology Disease Area Strategy Leader (from June 2006) and as Vice President of Translational Sciences in the Neuroscience iMed unit (from September 2010). In the second role she was a member of the RAMT, and in the third role she was a member of the Neuroscience iMed Leadership Team which replaced it. She was involved in the BACE project from early 2005 until she left AstraZeneca, and in May 2012 she became the Global Project Lead for the project. Originally she was based at Södertälje, but from July 2012 onwards she was based in Cambridge, Massachusetts. She is currently Vice President of the Alzheimer's Discovery & Development Group at Biogen.

ix) **Dr Kumar Srinivasan** obtained a PhD in Organic Chemistry from Case Western Reserve University in 1992 and carried out post-doctoral research at California Institute of Technology from 1992 to 1993. After a period as a research scientist, he obtained an MBA from University of Chicago. After working as an executive for a number of pharmaceutical companies, he joined AstraZeneca in April 2012 as Vice-President, Business Development and Licensing in Cambridge, Massachusetts. He is currently Vice-President, Head of Scientific Partnering and Alliances at AstraZeneca Pharmaceuticals LP.

x) Mr Conor Johnston is a solicitor who has been employed by AstraZeneca as Chief Counsel, Neuroscience, Innovative Medicines and Early Development since September 2012. Prior to that, he was employed by MedImmune, AstraZeneca's biologics research and development arm.

xi) Dr Peter Söderman obtained a BASc degree in Organic Chemistry from Stockholm University in 1993 and a PhD in the same subject from the same institution in 1999. From 1999 to 2000 he undertook post-doctoral work at Massachusetts Institute of Technology. He was employed by AstraZeneca from October 2000 to October 2012 successively as Senior Research Scientist, acting Chemistry Project Leader, Team Leader and Chemistry Project Leader. He worked on the BACE project from September 2007 onwards. Since May 2013 he has been employed by Karolinska University Hospital as Innovation Program Manager. Like Mr Berg, Dr Söderman had less recollection of the events than some of the other witnesses.

xii) Dr Joerg Holenz obtained a BSc in Chemistry from the University of Cologne in 1990 and a PhD from the Julius-Maximilians-University of Würzburg in 1997. He was employed by AstraZeneca from August 2006 to June 2016 successively as Chemistry Project Leader, Team Leader in the Lead Optimisation department and head of Lead Generation at Södertälje and then Director for Discovery and Preclinical Sciences in Cambridge, Massachusetts. Since June 2016 he has been employed by GlaxoSmithKline as Head of Neuroscience Virtual Proof-of-Concept Discovery Performance Unit.

xiii) Ms Jenny Viklund obtained an MSc in Molecular Biotechnology from Uppsala University in 2002. She was employed by AstraZeneca from 2002 to 2012, initially as Research Scientist and then as Senior Research Scientist in the Computational Chemistry group at Södertälje. Since 2012 she has been employed by Sprint Bioscience, initially as Associate Principal Scientist and latterly as Principal Scientist, and thus she was an independent witness. She was cross-examined at considerable length about her work at the computational chemistry workshop in September 2005. As she accepted, some of her evidence was direct recollection and some was reconstruction based partly on memory, partly on the documents and partly on her working methods. Counsel for Astex submitted that her evidence was unreliable and that the documentary evidence was a more reliable guide to what she had done. Ms Viklund gave her evidence with unchallenged sincerity and considerable conviction, but I accept that that does not obviate the need for a careful assessment of it in the light of the documentary evidence and the inherent probabilities. It is convenient to note at this point, however, that her evidence does not stand alone. On the contrary, parts of it were supported by the evidence of Dr Kolmodin and (to a lesser extent) Mr Berg. Moreover, as I will explain, the documentary record is not as unequivocal as counsel for Astex submitted.

1. In addition, AstraZeneca relied on two witness statements made by Dr Mark Sylvester, whose evidence was not challenged by Astex.

*Missing witnesses*

1. A number of potential witnesses on both sides were not called. Astex did not call any of its scientists who worked on the BACE project other than Dr Murray, and in particular did not call Dr Miles Congreve or Dr Gianni Chessari despite the fact that at one stage considerable reliance was placed by Astex on laboratory notebook entries of theirs. No explanation was given for this, but counsel for AstraZeneca did not suggest that any adverse inference should be drawn from it, and in any event the points were not pursued by Astex.
2. AstraZeneca employed a large number of people on the BACE project at different times and in different places. Understandably, AstraZeneca did not attempt to call all of them, which would have been wholly impractical as well as disproportionate. Counsel for Astex drew attention in his written opening submissions to the fact that AstraZeneca had not called Johanna Fälting, Mark Farmery, Patrik Renblad or Michael Vestling. None of those persons remains employed by AstraZeneca and they are all resident outside the United Kingdom. Counsel for Astex nevertheless submitted in his closing submissions that I should draw an adverse inference from AstraZeneca's failure to adduce evidence from Dr Fälting, Dr Farmery and Mr Renblad, despite the fact that AstraZeneca contends that all three were mistaken in believing that CD1, and that Dr Fälting and Dr Farmery were mistaken in believing that CD2, was a Collaboration Compound. The grounds upon which he submitted that the adverse inference should be drawn were that (i) AstraZeneca had not established by evidence that the individuals had declined to co-operate with them and (ii) AstraZeneca had not established that they were resident in countries which did not have procedures for taking evidence in support of foreign witnesses.
3. I do not accept this submission. So far as point (i) is concerned, AstraZeneca's solicitors informed Astex's solicitors in correspondence that AstraZeneca had contacted Dr Fälting, Dr Farmery and Dr Vestlng, but they had declined to be called as witnesses, while it had not contacted Mr Renblad. I see no need for this to be confirmed by a witness statement. Moreover, Astex's solicitors revealed that they had contacted Dr Fälting and Dr Farmery, but both had declined to assist. That tends to confirm that they did not want to be involved. As for point (ii), I find it extraordinary that it can be suggested that an adverse inference should drawn against a party because that party has not applied for letters rogatory to be sent to a foreign court to compel a witness resident abroad to give evidence. That would add a new cost and terror to litigation in this country, and I decline to do so. In any event, I do not see why an adverse inference should be drawn in this case: it is clear from the evidence that Dr Fälting and Dr Farmery believed that CD1 and CD2 were Collaboration Compounds, but it is also clear that they did not have first-hand knowledge of the derivation of CD1 and CD2, still less did they have access to all the contemporaneous documents. Given that I have evidence from witnesses called by AstraZeneca who did have first-hand knowledge, and access to the contemporaneous documents, an explanation by Dr Fälting and Dr Farmery as to the reasons for their belief would be of little weight. Furthermore, as discussed below, the key decision maker in relation to CD1 was Dr Angst. As for Mr Renblad, it is unlikely that he had any real knowledge about the status of CD1. As for CD2, no payments were made in relation to it, and Dr Budd, Dr Srinivasan and Mr Johnston all gave evidence about the communications which AstraZeneca made to Astex about it.

The expert witnesses

1. On 18 April 2016 Chief Master Marsh made an order for directions which gave each party permission to call one expert witness in the field of pharmaceutical drug discovery. As I understand it, that aspect of the order was made by consent. The order also provided for sequential service of experts' reports, with (somewhat unusually) AstraZeneca's expert's report being served first. Perhaps partly as a result, AstraZeneca's expert ended up serving three expert reports and Astex's expert two. I am concerned that, through no fault of the experts, a considerable amount of money was wasted upon the preparation of these reports. I do not doubt that there was a role for expert evidence in this case, in particular to educate the court as to the technical background and to the general processes of drug discovery as at the date of the Agreement. But the parties do not appear clearly to have identified the issues which the experts should address in their reports prior to instructing their experts. Moreover, both sides instructed their expert to consider the history of the way in which CD1 and CD2 were developed as revealed by the witness statements and (at least to some extent) the contemporaneous documents. Given that neither expert professed expertise as a forensic investigator, such evidence was of doubtful admissibility. Astex's expert was also instructed to set out his interpretation of particular clauses and phrases in the Agreement, evidence which was plainly inadmissible. Even if it was admissible, the cost of preparing this evidence will certainly have been disproportionate to its value in resolving the issues.
2. At the beginning of the trial I was presented with a proposed trial timetable which envisaged the experts giving oral evidence for a total of three days. As I pointed out, as if that was not bad enough, if the experts were to be cross-examined in detail about the history, they would not only need to read those contemporaneous documents which they had not already read, but also need either to sit through, or read the transcripts of, the oral evidence of many of the factual witnesses. The costs of these exercises would again be considerable, and disproportionate to their value in resolving the issues given that I was to have first-hand evidence from many of the key scientists involved in the development of CD1 and CD2. I therefore suggested that oral expert evidence be limited to, say, half a day each. AstraZeneca subsequently proposed that cross-examination of the experts be dispensed with. Astex did not accept that proposal, but did agree that the scope of the oral expert evidence should be limited to certain topics. Regrettably, I later discovered that this was not sufficient for the experts to be stood down from attending the entire trial. After the conclusion of the factual evidence and before the experts were called, I discussed with the parties the scope of cross-examination. Apart from directing that the oral evidence be limited to half a day each, I did not formally restrict the scope of cross-examination, but I did make it clear that I was unlikely to be assisted by cross-examination directed to some of the topics proposed. I am happy to record that both leading counsel completed their respective cross-examinations in less than the time allowed. Despite that, I am very concerned the overall cost of the expert evidence will have been grossly disproportionate.
3. The moral of the story, which is not a new one, is that what is required is clear identification of the issues which experts are going to be asked to address before the experts are instructed. Only if the issues are clearly identified is it possible to ascertain whether the experts can give evidence directed to those issues which is (a) admissible and (b) likely to be of sufficient weight for the cost of preparing their evidence to be proportionate to what is at stake.
4. **Astex's expert was Sir Simon Campbell** CBE, FRS, FMedSci. Sir Simon obtained a BSc in Chemistry from the University of Birmingham in 1962 and a PhD in the same subject from the same institution in 1965. From 1965 to 1970 he undertook post-doctoral research at Birmingham, Universidad Tecnica Federico Santa Maria and Stanford University. From 1970 to 1972 he was employed as a Research Fellow by the US National Academy of Sciences and as a Lecturer by the Universidade de Sao Paulo. From 1972 to 1998 he was employed by Pfizer in positions of increasing seniority, beginning as Staff Chemist and ending as Senior Vice-President, Worldwide Discovery and R&D Europe. Since then, he has acted as a consultant, a scientific advisory board member for a number of companies and a member of various committees and organisations. He has over 70 publications and over 50 patent applications to his name. He has received a number of awards, and was knighted for services to Chemistry in 2015.
5. **AstraZeneca's expert was Dr Christopher Hill**. Dr Hill obtained a BSc in Chemistry from the University of Manchester in 1981 and a PhD from University of Manchester Institute of Science and Technology in 1984. From October 1984 to September 1985 he undertook post-doctoral research at the Institute de Chemie des Substances Naturelles. From 1985 to 2001 to he was employed by F. Hoffman La Roche in progressively senior posts, interrupted by a short spell as Head of Organic Synthesis at Parke Davis Neuroscience Research Centre in 1993-94. From 2001 to 2007 he was employed by Organon International as Head of Medicinal Chemistry. He continued in this role after Organon's merger with Schering-Plough in 2007 and after Schering-Plough's merger with Merck & Co Inc to form Merck Sharp Dohme ("MSD") in 2009. In 2010 he became Site Head at MSD's Boston, Massachusetts facility. From 2011 to 2015 he was Head of Global Chemistry for MSD. Since 2016 he has been an independent consultant.
6. This is not a case in which it is necessary for me to decide which of the two experts' evidence I prefer, since in my view neither of them was in a position to give any evidence of real weight on the points which matter. Nevertheless, I would, if necessary, give more weight to Dr Hill's evidence for the following reasons.
7. First, notwithstanding Sir Simon's eminence, Dr Hill had the advantages, for the purposes of this case, of having (i) worked for a wider range of pharmaceutical companies than Sir Simon, (ii) done so during the relevant period and (iii) worked on a BACE inhibitor project from 2007 that led to the development by MSD of a candidate drug which was progressed to Phase III trials (and continues to be studied for pre-symptomatic indications).
8. Secondly, whereas Dr Hill's instructions asked him to consider the historical development of CD1 and CD2 as it was described by the factual witnesses, Sir Simon's instructions asked him (or at least were understood by him as asking him) to consider with the benefit of hindsight whether CD1 and CD2 could be "traced back" to compounds identified during the Collaboration Term. Sir Simon confirmed that he had made no attempt to put himself into the shoes of the persons who had done the work, with the knowledge and aims that they had had, nor had he attempted to distinguish between direct results and indirect results. As will appear, I consider that the approach Dr Hill was asked to take is more consistent with that required by the Agreement than the approach adopted by Sir Simon.
9. Thirdly, Sir Simon was led by his instructions to question the accounts given by some of the AstraZeneca witnesses in their witness statements, but without having fully understood what they had done. As counsel for AstraZeneca pointed out, an example of this is his failure properly to recognise the contribution made by Dr Kolmodin's modelling work.
10. Fourthly, Sir Simon focussed almost exclusively in his reports upon the potency of the compounds as measured by the FRET assay (as to which, see below), whereas AstraZeneca's scientists had to address many other properties of the compounds in order to arrive at CD1 and CD2. In my view, it is clear from the factual and documentary evidence that important aspects of the development of CD1 and CD2 were driven by properties and considerations other than potency as measured by the FRET assay (or, indeed, as measured by other assays such as BIACore). Moreover, as Dr Kolmodin explained, structure-based design only gave the boundary conditions for one of the properties that needed to be optimised, namely the fit of the compound to the target in the *in vitro* assays (giving rise to its potency). Other properties needed to be explored by trial and error, trying to making rational designs in order to test hypotheses. For example, the structure of the BACE protein is not relevant to the permeability of the compound.

Factual background to the Agreement

*Technical background*

1. Much of the general technical background is set out in my judgment in *Eli Lilly and Co v Janssen Alzheimer Immunotherapy* [[2013] EWHC 1737 (Pat)](http://www.bailii.org/ew/cases/EWHC/Patents/2013/1737.html%22%20%5Co%20%22Link%20to%20BAILII%20version) at [12]-[42], which Dr Hill referred to in his first report and which I will take as read. As Dr Hill noted, those passages considered the position as at 2 December 1997. It is therefore necessary to say a little about the subsequent development of the state of the art.
2. In late 1999 and early 2000, a number of groups independently published the first indications that the long-sought ß-secretase which proteolytically cleaved APP was a transmembrane aspartic protease. The novel protein was cloned and characterised, and named BACE. BACE was later termed "BACE-1" when another human homolog, "BACE-2", also with a transmembrane segment, was identified. Other names for BACE-1 that were coined at around this time were "ASP-2" (from aspartic protease 2 or aspartyl protease 2) and "memapsin-2" (from membrane associated aspartic protease 2 according to enzyme nomenclature). For convenience, I shall refer to it throughout as BACE.
3. BACE was found in subsequent studies to be the major ß-secretase responsible for Aß generation in the brain. BACE cleaves at the ß and also the ß' site (between amino acids 10 and 11 of Aß) of APP. BACE messenger RNA has high expression levels in the mammalian brain and targeted deletion of BACE in APP transgenic mice abolishes the production and deposition of Aß. Conversely, overexpression of BACE-1 in a number of cell lines leads to enhanced Aß production. By mid-2000, BACE was recognised as the relevant ß-site APP processing enzyme, and it had been shown that the absence of BACE did not pose serious consequences for experimental animals, which, in turn, suggested that targeting BACE for inhibition in AD therapy may be tolerable in humans.
4. Furthermore, **BACE, as an aspartic protease**, was an encouraging (albeit difficult) target since a precedent had already been set with the successful development of inhibitor molecules to human immunodeficiency virus ("HIV") protease, also an aspartic protease. These included the HIV protease inhibitors saquinavir, indinavir, nelfinavir, amprenavir and ritonavir developed in the mid- to late-1990s. Knowledge was also available on renin inhibitors, but at the time of the Collaboration no drugs had yet been approved for this aspartyl protease.
5. A key step in drug design is to gain an understanding of the structure of the target molecule. Furthermore, when the target is an enzyme or other molecule with a catalytic or functionally active site, a detailed understanding of the chemical and physical properties of the active site will greatly inform drug design to target the critical region.
6. The crystal structure of BACE was described by Hong *et al.* in a series of papers published from 2000 onwards. A long active-site cleft was identified, and further studies provided important molecular insights into the ability of ligands and inhibitors to interact with the cleft. In particular, it was discovered that the reactive centre or RC had two aspartic acid residues (also referred to as "catalytic aspartates"), asp228 and asp32, which interacted with peptide inhibitors by means of hydrogen bonds, and that there were a number of pockets adjacent to the RC, including the S1 and S3 pockets. (During the Collaboration Term, additional pockets adjacent to the S1 and S3 pockets were identified as having roles to play which were later given the labels S'-sub and S3-sub.)

*Drug discovery*

1. As the evidence in this case amply confirms, the process of discovering a new drug, in the sense of identifying a substance which appears to have both the desired biological activity and other suitable properties for administration to human beings, is an extremely lengthy, arduous and expensive process.
2. The experts provided some general background to the process. There was little disagreement between them so far as the process is concerned, as opposed to the language in which it is described. It is important to note two points.
3. First, since the key disputes concerned the meaning of terms used in the Agreement, and since the experts were agreed that none of the key terms were recognised terms of art with fixed meanings in February 2003, their evidence about the meaning of those terms is either inadmissible or of little weight, since the key question is how those terms would have been understood in the context of the Agreement.
4. Secondly, and perhaps even more importantly, many of the terms in question were ones which the parties and their employees used at the time in other contexts. It cannot be assumed that such terms were understood in those contexts in precisely the same way as they would have been understood in the context of the Agreement. This is a point which has to be kept constantly in mind when considering the contemporaneous documents and the evidence of the factual witnesses. To be clear, it is sometimes necessary to understand what a particular witness meant by a particular term in a particular document, but this is only because of its relevance to the fact-finding process and not because it sheds any light on the interpretation of the Agreement.
5. With those caveats, the process of drug discovery as it was generally understood in pharmaceutical companies in February 2003 may be described as follows.
6. Drug discovery typically starts with screening known compounds for activity, or designing, making and testing new ones, or both. In the past, screening would typically involve some form of *in vitro* assay which was used as a surrogate for activity in the body, or in some cases more than one kind of assay. By 2003, other screening techniques were being adopted, including a number which depended on physical methods such as NMR (Nuclear Magnetic Resonance), X-ray crystallography and SPR (Surface Plasmon Resonance), to detect binding or "affinity" between the compound being screened and the target. In addition, screening could be carried out by "virtual" methods, in particular using "docking" software which would enable a computational chemist to visualise the three-dimensional interaction between the compound being screened and the target.
7. It is common to refer to compounds which display sufficient activity in such screening as "hits". Generally, it is desirable to identify multiple hits with a diversity of chemical structures. Ideally, this will enable the identification of a "pharmacophore", meaning a set of features (types of atoms, bonds, geometry and relative positions in space) of a ligand (a molecule which binds to a receptor) which enable it to interact with its target.
8. **The next step is a "lead generation" phase**, which seeks to identify high-quality chemical starting points ("leads") for future optimisation ("lead optimisation"). Ideally, it is desirable to identify multiple leads due to the high rate of attrition in later phases. During lead generation, the developers will start to explore other desired properties of the compound. In the present case, these include, among other things, its selectivity (the extent to which it binds to BACE rather than other aspartyl proteases), its cell permeability (its ability to enter cells, which depends in part on its acidity or basicity as measured by the negative logarithm of the dissociation constant, pKa), its ability to cross the blood-brain barrier ("BBB"), its hERG activity (hERG being a gene which codes for a protein which forms a subunit of a potassium ion channel which contributes to the electrical activity of the heart, high hERG activity being undesirable) and its CYP activity (Cytochrome P, particularly Cytochrome P450 3A4, an enzyme found in the liver and intestine which removes toxins, including drugs, from the body).
9. Usually, each lead will be elaborated into a series of compounds based on a common "core" or "scaffold" of the molecule, such that a series will have some common structural and functional attributes (e.g. share a common structure-activity relationship or SAR or, better, share common structure-property relationships or SPRs). **The goal of lead generation is to end up with sufficient confidence in each series of compounds to move on to lead optimisation**.
10. There was some disagreement between the experts on the extent to which lead generation activities are distinct from lead optimisation activities. Sir Simon said that he had not experienced a rigid division between the two, but Dr Hill's experience at Organon and MSD was that projects were routinely separated into lead generation and lead optimisation activities, with different chemists dedicated to those phases. Certainly, **AstraZeneca had dedicated teams for each of these activities, and the Research Plan identifies distinct phases which mirrored AstraZeneca's internal phases** (which, it should be noted, subdivided lead generation into hit identification and lead identification).
11. In order for a lead series to make the transition to lead optimisation, there should be enough understanding of relevant properties and sufficient evidence to show that they can be improved by subsequent optimisation. A lead series will contain one or more exemplar compounds which meet pre-defined generic properties and activities, subject to some flexibility so long as there is sufficient evidence of scope for optimisation.
12. Even after one or more series has made the transition into lead optimisation, lead generation activities will typically continue in order to provide back-up series. Dr Hill's evidence was that the generation of new hits and lead series is inherently a lead generation activity regardless of the phase of any existing series in the discovery project at that time.
13. A term which featured quite extensively in the evidence is "scaffold hopping". This is a term which was becoming prevalent at the time of the collaboration between Astex and AstraZeneca, although the activity it describes was not a new one. Although it features in some of the contemporaneous documents, it does not appear to have been a term that was in regular use in Södertälje. The term must be treated with caution, because different people used it to mean slightly different things. Broadly speaking, however, it refers to an attempt to generate a new hit or lead series by replacing the core or scaffold of one series of compounds with a different core or scaffold while retaining the binding groups of the original compound or series in the same spatial position and orientation. It is hoped that this will enable some desirable properties which have been established (such as binding affinity) to be retained, while enabling other properties (such as permeability) to be improved. It can result, however, in the loss of the desirable properties of the original series.
14. **Lead optimisation** is a complex, iterative process of improving lead compounds, paying attention to multiple properties in parallel, towards a more stringent and extensive set of criteria that justify progression to candidate drug selection and preclinical development.
15. As optimisation progresses, the molecular weight and lipophilicity of molecules tends to increase as compounds are elaborated in order to give desirable properties. However, if compounds become too large and lipophilic, they tend not to be well-absorbed and "drug-like" when administered orally. There is a well-known rule of thumb known as "Lipinski's rule of five", defining the typical characteristics of drug-like molecules. By comparison, lead compounds are smaller and simpler, and a "rule of three" defines typical properties of such molecules.
16. Drug discovery projects like the BACE project involve the work of a number of different kinds of scientist, including the following:

i) medicinal chemists, whose expertise lies in combining knowledge of organic chemistry with biological knowledge to identify and/or design chemical compounds with medically desirable properties;

ii) computational chemists, whose expertise lies in analysing large datasets to extract information which is useful in the identification and/or design of compounds, in molecular modelling and in mathematical modelling of the properties of compounds to enable predictions to be made; and

iii) synthetic chemists, whose expertise lies in devising methods to synthesise desired molecules, which involves using their knowledge of chemical reactions to devise synthetic routes from an available starting material.

1. In addition to the kinds of scientists listed above, input is likely to be required from scientists and/or technicians who have expertise in the performance of assays and screening methods of various kinds to test the properties of compounds which have been synthesised during the course of the project. In the case of the BACE project, these included the following methods of measuring the activity of the compounds in binding to BACE:

i) NMR screening;

ii) X-ray crystallography;

iii) SPR screening, in particular using assays provided by a company called BIACore;

iv) FRET (Fluorescence or Förster Resonance Energy Transfer) assays – an *in vitro* test of enzyme inhibition in solution which can be used to determine the potency of the test compound as expressed by its IC50 (half maximal inhibitory concentration - the lower the IC50, the higher the potency);

v) cellular assays – an *in vitro* test of activity in cell cultures; and

vi) tests in transgenic mice – an *in vivo* test of activity using markers in laboratory animals.

1. In addition, a number of assays of other properties, such as permeability, hERG and CYP activity, were also used. Thus permeability was measured by an assay called the "Caco-2" cell line assay.

Work done by each party on BACE prior to the collaboration

1. Although neither party was aware of any details of the work done by the other on BACE prior to entering into the Agreement, this is a convenient juncture at which to describe that work. As explained below, the work which the parties had done separately before the Agreement formed the initial basis for the collaborative work they undertook after the Agreement.

*AstraZeneca's work*

1. AstraZeneca's BACE project appears to have been started at its site at Wilmington in 1999 with the development of assays. By 2000 the Project Leader was Dr David Aharony. The BACE chemistry team at Wilmington was formed in about May 2000, with Dr Edwards as the Lead Chemist. He remained in this role until Wilmington ceased its chemistry efforts in May 2005, at which point the transfer of the BACE project to Södertälje was complete. Dr Edwards again acted as Lead Chemist when Wilmington undertook a further discrete period of chemistry on the project to assist Södertälje after the transfer from October 2005 to July 2006.
2. Until the middle of 2002, the team investigated several approaches for hit identification, including high-throughput screening, but without identifying any viable leads. In spring 2002 efforts began on NMR screening of existing fragment libraries, using the resources of the SCL in Mölndal. The aim of fragment-based screening is to identify the binding of small molecules (referred to as "fragments") to the target protein, even if their binding is too weak to detect in conventional affinity assays. A weak-binding fragment can then serve as a building-block for elaboration into a larger, drug-like molecule with higher affinity and appropriate properties. The SCL employed NMR spectroscopy to carry out this screening, which (like X-ray crystallography) had the advantage of enabling non-specific binders to be avoided.
3. The NMR screening resulted in the second half of 2002 in the emergence of weak-binding affinity hits which were referred to by the Wilmington team as "AFFITs". Because of the weak binding, AstraZeneca was not in a position to infer an SAR at that stage.
4. Dr Kolmodin became involved at Mölndal in late 2002, where she used computational tools to select further compounds for NMR screening from AstraZeneca's compound collection and from among commercially available compounds. NMR hits were validated using BIACore assays to determine binding affinity, and FRET enzyme inhibition assays to determine IC50 potency. Further validation was done by X-ray crystallography of the fragments bound to endothiapepsin, an aspartic protease which AstraZeneca was using as a surrogate for BACE at that time.
5. In addition to the work being done in Mölndal, the Wilmington team used the hits identified by the SCL to interrogate AstraZeneca's database to try to identify any additional analogues of those hits (referred to as "database mining") that would allow them to establish an SAR. By July 2002 AstraZeneca had identified the first isocytosine hit. In the second half of 2002 the Wilmington team started making chemical modifications of some of the NMR hits, again with a view to establishing an SAR.
6. One of the compounds selected for this purpose was a 3-N-methylated, 6-phenylethyl isocytosine with the reference number M695756. In November 2002 it was discovered that M695756 had significantly increased activity relative to its non-methylated analogue. As result, Wilmington incorporated this feature into a lot of its subsequent optimisation efforts. This was also an early use of a B ring as a substituent.
7. By March 2003 the top three validated hit series identified by AstraZeneca were the isocytosines ("ICs"), aminobenzimidazoles and isothioureas. The AstraZeneca chemists noticed that all three series interacted with the two aspartic acid residues in BACE in a similar way. The structure of the ICs is shown below.



*Astex's work*

1. **Before the collaboration, Astex developed a technique for screening fragments against crystal structures of target proteins using high-throughput crystallography ("HTx"), which it called Pyramid**. In addition, Astex had developed a software tool called AstexViewer which enabled the visualisation of chemical structures, molecular surfaces, protein schematics and crystallographic information. Astex made this software available for download from its website in 2002. Astex also developed a further web-based software application called "the overlay page", which operated in conjunction with AstexViewer and which could be used to store and share information about the crystal structures of compounds. Looking ahead, Astex used the overlay page to share information about crystal structures with AstraZeneca on the BACE project.
2. **By April 2002 Astex had obtained a crystal structure of unbound *(apo*-) BACE**. Between May 2002 and March 2003 Astex synthesised about 150 compounds. In July 2002 Dr Murray took over leadership of the project. By December 2002 Astex had completed screening its proprietary fragment library using Pyramid. By March 2003 Astex had obtained about 25 crystal structures of compounds from various sources bound to BACE. By this means Astex identified three series of hits, the aminopyridines ("APs"), aminoquinolines and piperidines. Like AstraZeneca, Astex noticed that its series interacted with asp228 and asp32 in a similar way. The structure of the APs is shown below.



The parties' reasons for entering into the collaboration

1. Although the three-dimensional structure of BACE had been determined, and two BACE crystal structures bound to peptide inhibitors had been published by 2003, **AstraZeneca had been unable to obtain crystal structures of *apo*- BACE or of BACE bound to non-peptide fragments**. That was why it was using endothiapepsin for crystallography. By contrast, Astex had succeeded in crystallising *apo*-BACE and was using it to identify hits. AstraZeneca's main reason for entering into the collaboration with Astex was to gain access to Astex's *apo*-BACE crystal, and hence the ability to obtain crystal structures of ligands bound to BACE (obtained after "soaking" the ligands into the already-crystallised protein). That would enable solid structure-based design to be carried out. A secondary reason was to gain access to Astex's Pyramid technology for HTx. While Astex's expertise in fragment-based drug discovery and structure-based drug design was welcome, AstraZeneca already had this expertise, and it was not a significant factor in AstraZeneca's decision to work with Astex.
2. The collaboration gave Astex the chance to work with a larger and better-resourced partner. More specifically, it provided funding for Astex of up to US$1,050,000 with the prospect of Program Milestone and Development Milestone payments if certain things were achieved and the further prospect of royalties in the event of sales of a Licensed Product. In addition, Astex gained certain other potential benefits, such as the right to exploit Results for Program-Independent Activities.
3. Discussions about entering into the collaboration began in spring 2002, and became serious in summer 2002. After fairly lengthy negotiations, the Agreement was signed on 21 February 2003.

Interpretation of the Agreement

1. There is no dispute as to the principles to be applied in interpreting the Agreement. They have been considered by the House of Lords and the Supreme Court in a series of cases culminating in the recent decision of the Supreme Court in *Wood v Capita Insurance Services Ltd* [[2017] UKSC 24](http://www.bailii.org/uk/cases/UKSC/2017/24.html%22%20%5Co%20%22Link%20to%20BAILII%20version), [[2017] 2 WLR 1095](http://www.bailii.org/cgi-bin/redirect.cgi?path=/uk/cases/UKSC/2017/24.html). In short, the court's task is to ascertain the objective meaning of the language which the parties have chosen to express their agreement when read in the context of the factual background available to the parties at the time of the agreement, excluding prior negotiations.
2. There are four main issues of interpretation. The first concerns the duration of the Program. The second concerns the selection of Hits, Leads and CDs. The third concerns the definition of Collaboration Compound in Section 1.7. The fourth concerns the question of whether, and if so in what circumstances, the Agreement is capable of expiring in the absence of termination.

*The duration of the Program*

1. AstraZeneca contends that the duration of the Program under the Agreement is the same as the duration of the Collaboration Term. Astex disputes this. Although the Agreement expressly provides for the ending of the Collaboration Term in Sections 3.1 and 14.2, there is no comparable provision in the case of the Program.
2. The nearest is Section 1.32, but the parties are divided as to the correct reading of that provision. **AstraZeneca** contends that the final clause "**which thereafter may be continued by or on behalf of ASTRAZENECA alone**" qualifies the immediately preceding noun "the Project". The effect of this reading is that **the Program** is something that can only be performed by the parties in collaboration during the Collaboration Term; whereas **the Project** is something that may be continued by AstraZeneca on its own after the Collaboration Term. **Astex** contends that the final clause is part of the definition of "Program". The effect of this reading is that **the Program** is something that can both be performed by the parties in collaboration during the Collaboration Term and be continued by AstraZeneca on its own after the Collaboration Term.
3. In my view both readings of Section 1.32 are possible ones, in the sense that I do not consider that the wording compels either reading. One difficulty with Astex's reading of Section 1.32, however, is that it makes the words "as part of the Project" redundant. By contrast, the inclusion of those words serves a clear purpose on AstraZeneca's reading. This is a specific instance of a more general point, which is that the Agreement contains repeated references to both the Project and the Program. On AstraZeneca's interpretation, it is clear why those terms have been separately defined and why they are both used at different points in the Agreement. On Astex's interpretation, it is less clear why the Agreement refers to the Project at all.
4. AstraZeneca relies upon a considerable number of other provisions in the Agreement as supporting its interpretation of Section 1.32.
5. First, AstraZeneca points out that the "Project" is defined in the first recital and in Section 1.35 in a manner which makes it clear that it refers to AstraZeneca's extant project to develop a BACE inhibitor. Thus the Project is not a collaborative project. AstraZeneca contends that this supports the proposition that the Project could be continued by AstraZeneca alone after the Program ended.
6. Secondly, AstraZeneca points out that the fourth recital states that the Program is to be carried out "under" the Project. AstraZeneca again contends that this supports the proposition that the Project could be continued by AstraZeneca alone after the Program ended.
7. Thirdly, AstraZeneca relies upon Section 3.1, which provides for the JEC to oversee the activities under the Program. When this is read together with Section 3.7, which provides for the JEC to be dissolved at the end of the Collaboration Term, AstraZeneca contends that it is clear that the Program cannot continue after the end of the Collaboration Term.
8. Fourthly, AstraZeneca relies upon the fact that Section 3.7 expressly envisages AstraZeneca continuing the Project after the end of the Collaboration Term. AstraZeneca contends that this not only confirms that the Project could be continued by AstraZeneca after the Program ended, but also makes no sense if the Program could be continued by AstraZeneca on its own.
9. Fifthly, AstraZeneca relies upon Section 3.8, which expressly provides for AstraZeneca to provide Astex with Project reports after the dissolution of the JEC, that is to say, after the end of the Collaboration Term. Furthermore, it requires each party to nominate a point of contact for "all post-Program contacts". AstraZeneca contends that this makes it clear that the Project may continue after the end of the Program, that is to say, after the Collaboration Term.
10. Sixthly, AstraZeneca relies upon the fact that Section 14.2 provides that the Collaboration Term shall continue "for as long as Astex performs research activities under the Program". AstraZeneca contends that this supports the proposition that the Collaboration Term ends when the Program ends, while the Project may be continued by AstraZeneca after the Program and Collaboration Term have ended.
11. Seventhly, AstraZeneca relies upon clause 14.6.1, which expressly provides that the termination by AstraZeneca of the parties' collaboration on the Program ends the Collaboration Term. Furthermore, it also expressly provides that AstraZeneca will not be obliged to provide Astex with further reports on Results, which are defined in Section 1.38 as being "generated through work performed under the Program during the Collaboration Term". Still further, it envisages for AstraZeneca to provide limited Program *or Project* reports to Astex thereafter. AstraZeneca again contends that these provisions make it clear that the duration of the Program is co-extensive with that of the Collaboration Term, while the Project may continue afterwards.
12. Astex's response to many of these points is to say that the fact that the Project could continue did not prevent the Program continuing, but it accepts that on its interpretation Section 3.8 contains a drafting error, particularly in its reference to "post-Program" reports. In the case of Section 14.6.1, however, Astex positively relies upon this provision as supporting its interpretation, as discussed below.
13. Astex also relies upon certain other provisions in the Agreement as supporting its interpretation. First, Astex relies upon the definition of "Lead Compounds" in Section 1.23 as substances meeting "**the Lead criteria of the Program, which have been selected by the JEC, or after the Collaboration Term, by AstraZeneca as candidates for Lead Optimisation**". Astex contends that this shows that the Program can continue beyond the Collaboration Term. AstraZeneca's response is that the inclusion of the words "after the Collaboration Term" must be a **drafting error**. In support of this, AstraZeneca relies on the fact that this wording is not included in the definitions of "Hits" in Section 1.17 or "CD" in Section 1.6. AstraZeneca argues that **this drafting error cannot outweigh all the other indications in the Agreement that the Program ends with the Collaboration Term**.
14. Secondly, Astex points out that Section 1.38 defines Results by reference to "work performed under the Program during the Collaboration Term". Astex contends that it would be unnecessary to include reference to both the Program and the Collaboration Term if they were coextensive. AstraZeneca's response is that the parties could be doing other work during the Collaboration Term which would be caught if the definition were not limited to work under the Program. More generally, Astex contends that AstraZeneca's interpretation makes the use of the term Program in the Agreement redundant, but AstraZeneca replies that the two terms serve different purposes even though they are coterminous: one defines the ambit of the collaboration and the other defines the period for which it lasts.
15. Thirdly, Astex relies upon Section 2.9, which expressly provides that, after the end of the Collaboration Term, AstraZeneca may "select additional AFFITs, AFFIT Improvements and Collaboration Compounds for optimisation and/or clinical development", but must notify Astex. AstraZeneca's response is that this does not demonstrate that the Program continues beyond the Collaboration Term. As AstraZeneca points out, the expression "optimisation and/or clinical development" does not use any of the defined terms. As AstraZeneca also points out, it is not the case that Astex's only contractual interest after the end of the Collaboration Term lies in substances having the status of Collaboration Compounds. Given the provisions in particular of Section 5 of the Agreement, Astex would have a legitimate interest in being notified by AstraZeneca of optimisation and/or clinical development of AFFITs and AFFIT Improvements.
16. Fourthly, Astex relies upon Section 3.1, which requires all AFFITs, Hits and Leads generated up to the expiration of the Collaboration Term to be listed in Schedule 3.1. As AstraZeneca points out, however, such compounds would all be Collaboration Compounds. The list was clearly intended to provide a measure of certainty in that regard. This provision does not indicate that the Program continues after the Collaboration Term. Indeed, AstraZeneca contends that, when Section 3.1 is read together with Section 3.6, which requires all AFFITs, Hits, Leads and CDs nominated during the Collaboration Term to be recorded in the minutes of the JEC, they support the view that the Program ends with the Collaboration Term.
17. Fifthly, Astex relies upon Section 14.2 and 14.3. Astex's reliance upon Section 14.2 is puzzling, since it supports AstraZeneca's interpretation of the Agreement, and not Astex's. As for Section 14.3, Astex relies upon the fact that it enables AstraZeneca, if it decides that it is no longer desirable or feasible for it to pursue the Program, to terminate the entire Agreement. I fail to see how, whether on its own or in conjunction with Section 14.2, this supports the contention that the Program continues after the Collaboration Term.
18. Sixthly, Astex relies upon the fact that Section 14.6.1 envisages "Program … reports … limited to … whether the Program and/or Development Milestones have been met" being provided by AstraZeneca to Astex after the end of the Collaboration Term as showing that the Program continues. AstraZeneca counters that this simply allows for the possibility of a Program report being due at the time of termination and/or for Program and/or Development Milestones having been met at that time.
19. Seventhly, Astex relies upon the description of the Program in the Research Plan in Schedule 1.37 as suggesting that the Program could continue with only the involvement of AstraZeneca. As AstraZeneca points out, however, nothing in the Research Plan indicates that the Program continues after the Collaboration Term.
20. Finally, it remains for me to consider four more general points. First, AstraZeneca argues that the effect of Astex's interpretation is that the duration of the Program is coextensive with the duration of the Project, and that cannot be right. Astex disputes that this is necessarily so. If Astex were correct about this, however, it would lead to the consequence that the Collaboration Term, Program and Project could all have different durations. I consider that that is improbable.
21. Secondly, AstraZeneca argues that, if the Program did not end with the Collaboration Term, then it would continue indefinitely until the Agreement came to an end. AstraZeneca contends that this cannot be right, particularly if Astex is correct that the Agreement does not end until it is terminated (as to which, see below). Astex's response to this is the Program comes to **an end either when AstraZeneca ceases "pursuing research referable to the Results" (see Section 14.1) or once research within the Research Plan has ceased**. But this seems to confirm AstraZeneca's point, particularly given that Section 14.1 does not refer to the Program at all and is about the duration of the Agreement.
22. Thirdly, AstraZeneca contends that Astex's interpretation leads to considerable uncertainty as to the ownership of intellectual property generated after the end of the Collaboration Term. As AstraZeneca points out, Section 5 of the Agreement contains elaborate provisions with respect to intellectual property rights, summarised in paragraph 17 above, which depend on the definition of "Results" in Section 1.38. But that definition only applies to work performed both under the Program and during the Collaboration Term. Astex's answer to this is that there is no difficulty: AstraZeneca would naturally own all intellectual property generated by work on its own after the Collaboration Term. AstraZeneca's rejoinder is that that is too simplistic: what about, for example, an invention that relates to a Collaboration Compound?
23. Lastly, Astex contends that AstraZeneca's interpretation cannot have been intended, because it would enable AstraZeneca unilaterally to cut Astex out when nomination of a CD was close. AstraZeneca disputes that its interpretation has this effect, however. I do not propose to lengthen this judgment still further by going into the details of these arguments, which revolve around the MS4 and MS5 transitions in the Research Plan. It suffices to say that I agree with AstraZeneca that Astex's argument depends on a rather unreal scenario and that the JEC would be unlikely to bring the Program to an end if nomination of a CD was close (and AstraZeneca would be in breach of Section 2.1 if it tried to dictate such a conclusion).
24. As the preceding discussion demonstrates, there are arguments in favour of both interpretations. The conclusion I have reached is that the better view is that **the Agreement should be interpreted in the manner contended for by AstraZeneca**. **Astex's strongest point is Section 1.23**. but I agree with AstraZeneca that comparison with Sections 1.6 and 1.17 suggests that **the inclusion of the words "after the Collaboration Term" may have been a drafting error**. In any event, I consider that this point is outweighed by all the other provisions and considerations which support AstraZeneca's interpretation, whereas the other provisions and considerations relied upon by Astex carry less weight.

*The selection of Hits, Leads and CDs*

1. The definitions of Hits, Leads and CDs in Sections 1.17, 1.23 and 1.6, but not the definition of AFFIT in Section 1.2, all include the requirement that the compound has been "selected" by the JEC or by AstraZeneca as a candidate for Hit Optimisation or a candidate for Lead Optimisation or for clinical testing. Section 3.6 provides that all AFFITs, Hits, Leads and CDs "nominated" during the Collaboration Term shall be recorded in the minutes of the JEC, while Section 3.1 provides for a list of all AFFITs, Hits, Leads and CDs "generated" during the Collaboration Term to be drawn up as Schedule 3.1. Section 7.2(3) refers to "nomination" of a CD. The Research Plan in Schedule 1.37 uses both the term "selected" (paragraph 3.4) and the term "nominated" or "nomination" (paragraphs 1, 3.5 and 3.6).
2. AstraZeneca contends that Sections 1.17, 1.23 and 1.6 require a positive act of identification of the compound as having been selected for that purpose under the Agreement, and that (at least assuming AstraZeneca is right on the first issue), in the case of Hits and Leads, this selection or nomination must occur during the Collaboration Term. Astex disputes this. The significance of this issue is that, if AstraZeneca is correct, it potentially prevents Astex from relying upon certain compounds as Hits or Leads when it comes to applying the definition of Collaboration Compound.
3. In my judgment AstraZeneca is correct about this. Section 3.6 is clear that all Hits, Leads and CDs must be nominated and recorded in the minutes of the JEC. It makes sense that the parties wanted it to be clear whether or not a compound had been selected as a Hit, Lead or CD. The definitions in Sections 1.17, 1.23 and 1.6 are consistent with this, as is Section 3.1 and Section 7.2(3). For what it is worth, so is the requirement for "Endorsement by AZ" in paragraph 3.3 of the Research Plan in Schedule 1.37.
4. It is true that, as noted above, Section 1.2 does not require AFFITs to be selected, and in that respect it could be said that Section 3.6 is ill-drafted whereas the drafting of Section 3.1 is more apt. But as counsel for Astex himself submitted, AFFITs did not need to be selected, since they were to be identified by screening, whereas Hits and Leads did need to be selected. Furthermore, Section 1.2 is clear that an AFFIT may be selected as a Hit.
5. I should note that AstraZeneca accepts that, in the case of CDs, the selection or nomination can occur after the Collaboration Term. As I understand it, this is because the definition in Section 1.6 does not include any reference to the Program, whereas the definitions in Sections 1.17 and 1.23 do through their references to Hit Optimisation and Lead Optimisation as defined in Sections 1.18 and 1.24. In my view this does not detract from AstraZeneca's interpretation of Sections 1.17, 1.23 and 1.6, because, in the case of a CD, there is little room for dispute as to whether or not it has been selected for clinical testing. An alternative interpretation is that CDs do have to be selected or nominated during the Collaboration Term. As discussed below, this would not in itself bar Astex's claim, because a Licensed Product only has to contain a Collaboration Compound, it does not have to contain a CD (see Section 1.25).
6. Astex argues that it is not open to AstraZeneca to rely upon its own failure to nominate Hits and Leads after the end of the Collaboration Term because this would amount to reliance upon its own wrong. Astex puts this argument in two ways. First, Astex contends that a failure to select Hits and Leads would amount to a breach of Section 2.1. Secondly, Astex contends that this would amount to a breach of an implied term that neither party would prevent the other from performing. Either way, Astex contends that it is to be presumed that it was not the intention of the parties that either should be able to rely upon its own breach of duty to avoid the contract or to obtain a benefit under it.
7. I do not accept this argument. First, it is clear from Sections 3.1 and 3.6 that there is no requirement for AstraZeneca to nominate Hits and Leads after the end of the Collaboration Term. Secondly, in those circumstances, there is no basis for the contention that a failure to nominate Hits and Leads after the end of the Collaboration Term amounted to a breach of Section 2.1. Thirdly, it was not put to any of AstraZeneca's witnesses that AstraZeneca had acted in bad faith in failing to nominate Hits and Leads after the end of the Collaboration Term. This is not surprising because there would have been no basis for any such suggestion. After the end of the Collaboration Term, AstraZeneca simply got on with pursuing the Project. Astex never complained that AstraZeneca had ceased to nominate Hits and Leads, and on the contrary entered into the 2009 Agreement which provided for the list of AFFITs, Hits, Leads and CDs required by Section 3.1 of the Agreement. Fourthly, AstraZeneca did nothing to prevent Astex from performing the Agreement, still less did AstraZeneca do so in any way which amounted to a breach of an express or implied term of the Agreement. Lastly, even if AstraZeneca was in breach of an obligation to nominate Hits and Leads after the end of the Collaboration Term, I do not understand how that would assist Astex. Astex makes no claim against AstraZeneca for breach of such an obligation, and the commission of such a breach by AstraZeneca would not mean that any particular compounds would acquire the status of Hits or Leads for the purposes of Sections 1.17 and 1.23, and hence Section 1.7, despite not having been nominated.

***The definition of Collaboration Compound***

1. The definition of Collaboration Compound is central to the Agreement, and to this dispute, because it underpins the provisions for the payment of Program Milestones, Development Milestones and royalties on sales of Licensed Products. (It is perhaps worth noting that the compound does not have to be a CD for some of these purposes, such as royalties on Licensed Products, presumably because selection as a CD was under AstraZeneca's control.) The definition is plainly carefully drafted with a view to achieving as much certainty as possible. Moreover, on its face, the definition anticipates the possibility of a dispute, which the definition is clearly intended to enable to be resolved in a (relatively) simple and transparent manner.
2. The key part of the definition of Collaboration Compound is "**all Hits, Lead Compounds, CDs and other substances and structures discovered or identified as a direct result of AFFIT Optimisation, Hit Optimisation or Lead Optimisation**". It is convenient to analyse this definition in stages.
3. Before doing so, it is important to put the definition in context. An important aspect of the Agreement in this respect is that it envisages a structured Program as set out in the Research Plan consisting of a number of conceptually distinct and sequential phases: AFFIT Identification, Hit Identification, Lead Identification, Lead Optimisation, Pre-CD nomination and CD nomination. Pursuant to Section 3.1 of the Agreement, it is for the JEC to decide when each stage of the Program has been successfully completed and whether to proceed to the next stage. On the other hand, it is clear from paragraph 2 of the Research Plan that different activities, such as Hit or Lead Identification on the one hand and Lead Optimisation on the other hand can proceed in parallel.
4. *No AFFITs*. As the last sentence of Section 1.17 confirms, AFFITs are not within the definition of Collaboration Compound (unless and until selected as a Hit: see Section 1.2).
5. *Structure of the definition.* AstraZeneca reads the words "discovered or identified as a direct result of AFFIT Optimisation, Hit Optimisation or Lead Optimisation" as qualifying "other substances and structures", but not "all Hits, Lead Compounds, CDs". The effect of this is that the definition divides into two sub-classes:

i) The first sub-class is "all Hits, Lead Compounds, CDs" as defined in Sections 1.17, 1.23 and 1.6 respectively (and nominated pursuant to Section 3.6).

ii) The second sub-class is "other substances and structures discovered or identified as a direct result of AFFIT Optimisation, Hit Optimisation or Lead Optimisation".

1. Astex reads the words "discovered or identified as a direct result of AFFIT Optimisation, Hit Optimisation or Lead Optimisation" as qualifying both "all Hits, Lead Compounds, CDs" and "other substances and structures".
2. The difference between these readings is smaller than might at first appear, because the definition of "CD" requires that it be a Collaboration Compound. To that extent, the definition is circular.
3. Although the syntax of the definition supports Astex's reading, I have come to conclusion that, when it is read together with the other provisions of the Agreement, AstraZeneca's reading fits better.
4. *"Chemical structure modification"*. AFFIT Optimisation, Hit Optimisation and Lead Optimisation are defined in Sections 1.4, 1.18 and 1.24 respectively. Each of the definitions involves the expression "chemical structure modification". This expression was not a term of art with a settled meaning in February 2003, and thus it must be construed in context. There is no real dispute that it means modification of one or more chemical structures. AstraZeneca contends that, in context, it refers to modifications which have actually been made, rather than merely proposed. At one stage Astex appeared to dispute this, although by the end of the trial I think Astex had effectively conceded the point. In any event, in my judgment, AstraZeneca is correct, because in each definition the phrase "chemical structure modification" is followed by the words "performed as part of the Program".
5. To qualify as AFFIT Optimisation ("AO"), the chemical structure modification must be performed:

i) as part of the Program;

ii) starting from AFFITs; and

iii) aiming to generate optimised AFFIT structures that, together with AFFITs, form the bases for the identification of Hits.

1. Similarly, to qualify as Hit Optimisation ("HO"), the chemical structure modification must be performed:

i) as part of the Program;

ii) starting from a Hit; and

iii) aiming at the identification of compounds with properties meeting the Lead criteria defined in the Research Plan.

1. Again, to qualify as Lead Optimisation ("LO"), the chemical structure modification must be performed:

i) as part of the Program;

ii) starting from a Lead Compound; and

iii) aiming at the identification of compounds with properties meeting the CD criteria outlined in the Research Plan (which may be amended by AstraZeneca).

1. An important point to note is that, although the word "Optimisation" forms part of the labels "Hit Optimisation" and "Lead Optimisation", the word "optimisation" does not form part of any of the definitions in Sections 1.18 and 1.24. In case of Section 1.4, the word "optimisation" does not form part of the definition, but the word "optimised" does. Although a lot of ink was spilled in the witness statements, experts' reports and submissions on what amounted to "optimisation", in my view this is a distraction. The question is not whether a chemical structure modification can be described as having been performed for the purpose, in one sense or another, of optimising the properties of a compound or series of compounds, but whether it was performed with one of the specified aims.
2. *"Lead criteria" and "CD criteria"*. It is not entirely clear what is meant by the "Lead criteria (as defined in the Research Plan)" in Section 1.18, but it appears that this refers to the "Success criteria for completion of LI" in paragraph 3.3. As for the "CD criteria (as outlined in the Research Plan …)" in Section 1.24, this clearly refers to the "generic" criteria in paragraph 3.6, which were to be replaced by specific criteria by AstraZeneca during the Lead Optimisation stage.
3. *"A Hit" and "a Lead Compound"*. AstraZeneca relies on the fact that the definitions of HO and LO refer to starting from "a Hit" and "a Lead Compound". This gave rise to quite a lot of argument about whether what was referred to as "aggregate optimisation", meaning the optimisation of series of compounds as opposed to individual compounds, was covered by these definitions. I do not consider that this is a profitable question to try to answer at that level of abstraction. The right question is whether a compound has been discovered or identified as a direct result of HO or LO. That in turn involves asking whether there has been chemical structure modification starting from the specified starting point and with the specified aim. In my judgment, the specified starting point must be a specific compound, because Sections 1.18 and 1.24 refer to "starting from a Hit" and "starting from a Lead Compound", whereas by contrast Section 1.4 refers to "starting from AFFITs"; but that does not exclude the possibility that there may have been HO or LO starting from more than one Hit or more than one Lead.
4. In reaching this conclusion, I have not overlooked the fact that the parts of the Research Plan in Schedule 1.37 are expressed in terms of "chemical series" (see in particular paragraphs 3.2 and 3.3). I do not consider that this assists Astex, however. The Research Plan sets out the different phases of the Program that were planned. It uses slightly different terminology to the terminology employed in the Sections with which I am presently concerned, for example it does not use the terms AFFIT Optimisation or Hit Optimisation, but rather Hit Identification and Lead Identification, for a different purpose. If anything, the fact that the Research Plan refers to series of compounds tells against Astex's interpretation, because it shows that the parties were perfectly aware of that language, but chose not to use it in Sections 1.18 and 1.24.
5. "*Aiming to/at*". AstraZeneca contends that "aiming to/at" refers to the (subjective) intention (objectively assessed) of the scientists who performed the chemical structure modification: was their intention to identify compounds with properties meeting the Lead Criteria or meeting the CD criteria?
6. Astex contends that the assessment should be wholly objective, and not dependent upon the thought processes of the scientists involved. In the alternative, Astex contends that it is the corporate intention that matters, and not the intention of the individual scientists. (Indeed, Astex goes so far as to say that the scientists could be "involuntary participants".) Astex also contends that what matters is the overall purpose of the work, and not the immediate purpose of the chemical structure modification. In this regard, reliance was placed upon Lord Hoffmann's discussion of ends, means and consequences in *OBG Ltd v Allen* [[2007] UKHL 21](http://www.bailii.org/uk/cases/UKHL/2007/21.html%22%20%5Co%20%22Link%20to%20BAILII%20version), [2008] 1 AC 1](http://www.bailii.org/cgi-bin/redirect.cgi?path=/uk/cases/UKHL/2007/21.html) at [62]-[63].
7. In my judgment AstraZeneca's interpretation of Sections 1.18 and 1.24 is the more natural one. Furthermore, it is supported by the second sentence of Section 1.7, which provides that "the Parties' internal laboratory books and records from the relevant process through which such substance or structure was discovered shall serve as exclusive evidence" to resolve disputes. This indicates that the relevant enquiry is an historical enquiry into the discovery process as evidenced by the documentary records: what was done by the scientists involved, from what starting point, with what aim and with what result?
8. That said, I accept that a chemical structure modification may be undertaken both with an immediate purpose and with a broader or longer-term aim. Thus the modification may be made, say, with the immediate purpose of reducing the pKa of a compound, and thereby improving its permeability, and thus with the broader aim of identifying a compound which meets the Lead or CD criteria in that respect.
9. AstraZeneca also contends that this is not an enquiry into what can be deduced about the origins of a compound with the benefit of hindsight. I do not think that Astex disputed this point by the end of the trial, but in any event I agree with it.
10. *"Direct result"*. It is plain from the definition that it is not sufficient for a substance to be identified as an *indirect* result of AO, HO or LO. Other than that, the Agreement does not provide any guidance as what amounts to a "direct result". Accordingly, the purpose of this restriction must be deduced from the language used in Section 1.7 in the context of the Agreement as a whole.
11. AstraZeneca argues that, if the definition in Section 1.7 is considered as a whole, together with the other definitions considered above, the purpose of the inclusion of the second sub-class referred to in paragraph 124 above is reasonably clear. AstraZeneca suggests that there are two overlapping purposes. First, to provide a simple mechanism to identify compounds which are roughly equivalent to Hits, Leads or CDs without investigating whether all the detailed criteria have been met. Secondly, it caters for the possibility that the outcome of an attempt at AO, HO or LO is different from what was intended, for example if HO results in the identification of a compound that is later selected as a CD.
12. By contrast, Astex did not really engage in its submissions with the purpose of the "direct result" wording.
13. I accept the thrust of AstraZeneca's argument, but I would prefer to express the apparent purpose slightly differently. As I see it, the primary purpose is to cater for the possibility that a compound which has not been nominated as a Hit, Lead or CD during the Collaboration Term, and hence does not qualify as a Collaboration Compound by that route, is subsequently incorporated by AstraZeneca into a product which, if the compound were a Collaboration Compound, would constitute a Licensed Product, and to enable Astex to benefit from that in certain circumstances. Astex is only entitled to benefit, however, if the compound has been discovered or identified as a direct result of AO, HO or LO. The restriction to "direct result" was plainly intended to limit the reach of this provision to compounds which have a close connection with the AO, HO or LO work, as opposed to compounds with a more remote connection. When it is borne in mind that Section 1.7 envisages that disputes over whether compounds directly result from HO or LO should be resolved exclusively by reference to the laboratory notebooks and other records, it can be seen that the parties must have intended that the test should provide a reasonably bright-line rule.
14. Astex contends that "direct" does not connote a limited number of steps. In this regard, reliance was placed upon *Boiler Inspection and Insurance Company of Canada v Sherwin-Williams Company of Canada Ltd* [[1951] AC 319](http://www.bailii.org/cgi-bin/redirect.cgi?path=/uk/cases/UKPC/1951/1951_5.html" \o "Link to BAILII version), a case about an insurance policy. In my view that case is of little assistance in construing the Agreement, however. I consider that the court is required to make an evaluation of whether the result is one which is properly described as "direct". A result may conceivably be "direct" even though there was an intervening step; but the more steps there were, the less likely it is to be "direct".
15. Although quite a lot of ink was spilled in the witness statements and experts' reports in assessing the obviousness or inventiveness of particular steps in the processes by which CD1 and CD2 were developed, it was common ground between the parties at trial that this was irrelevant. I agree with Astex that the same goes for the question of whether particular steps were "breakthroughs" or "major advances".

*Expiration of the Agreement*

1. AstraZeneca contended in its Defence and Counterclaim that the Agreement had expired. Astex not only disputed this, but also disputed that the Agreement is capable of expiring (as opposed to being terminated). Although AstraZeneca accepted in its closing submissions that it had not established on the evidence that the Agreement had expired, there remained a dispute between the parties as to whether the Agreement is capable of expiring.
2. The Agreement expressly refers in at least two places to the "termination or expiration of the Agreement", namely in Sections 10.1 and 14.9. On the other hand, it has no set duration, and it contains no term which expressly provides for its expiration.
3. Section 14.1 provides that the Agreement "shall continue in full force and effect, unless earlier terminated … , during the Collaboration Term and thereafter for as long as ASTRAZENECA is pursuing research referable to the Results and/or clinical development of one or more Collaboration Compounds and/or commercialising Licensed Product …" AstraZeneca contends that it is implicit in Section 14.1 that the Agreement expires when AstraZeneca is no longer doing any of those three things. Furthermore, AstraZeneca contends, it is immaterial that AstraZeneca can terminate the Agreement in certain circumstances pursuant to Section 14.3.
4. Astex contends that the only way in which the Agreement can come to an end is if it is terminated.
5. In my judgment AstraZeneca's interpretation is the correct one. Astex's interpretation is inconsistent with the express words of Sections 10.1 and 14.9 and with what is implicit in Section 14.1. Moreover, Astex's interpretation has the consequence that the Agreement endures forever unless AstraZeneca terminates it. It is highly improbable that that can have been intended.

The facts concerning the development of CD1 and CD2

1. The facts concerning the development of CD1 and CD2 have to be considered in the context, first, of the work done during the Collaboration Term, and secondly, of subsequent events. The relevance of the subsequent events at this stage is that Astex relies upon them as shedding light backwards on the development of CD1 and CD2, although some of them also have relevance to AstraZeneca's counterclaim. I shall present my account topic by topic and chronologically in relation to each topic; but in making my findings of fact I have considered the story, and the evidence, as a whole. Given that I have 18 files of contemporaneous documents (printed double-sided, so equivalent to 36 files printed single-sided), and detailed and extensive written and oral evidence from 16 factual witnesses (plus two experts), I cannot possibly refer to more than a fraction of the material in this judgment, but I have taken into account everything to which my attention has been drawn. It should be appreciated that many more compounds were screened, synthesised and/or tested than I shall mention. It should also be appreciated that, particularly on the AstraZeneca side as the years wore on, the BACE project involved the work of a large number of people, many of whom I shall not mention.

*Work during the Collaboration Term*

1. *Discovery of the amidine motif*. The first meeting between the parties' principal scientists following the signature of the Agreement was at AstraZeneca's Wilmington site on **18 March 2003**, the day before the first meeting of the JEC on 19 March 2003. Dr Edwards' presentation at the meeting summarised where AstraZeneca had got to with its three series, and proposed that they were instances of an amidine-based aspartyl pharmacophore. Similarly, Dr Murray's presentation summarised Astex's work on its three series, and pointed out they interacted with the aspartates in BACE by means of hydrogen bonds formed, in the case of the APs and aminoquinolines, by amidine-like moieties. Both sides were struck by the presence of the amidine-like motif (or "amidine motif" for short) shown below in AstraZeneca's series and in two of Astex's series.



1. The illustration below shows, first, the structure of a compound with an amidine motif (as it happens, a DIHI), and secondly, a 3D representation of the nitrogen atoms of the amidine motif (in blue) forming hydrogen bonds with two pairs of oxygen atoms (in red) in asp32 and asp228 in the active site of BACE.





1. It was immediately recognised that **AstraZeneca and Astex had discovered a new aspartyl protease pharmacophore**. This caused considerable excitement on both sides. During a teleconference on **9 April 2003**, Dr Edwards proposed exploitation of this pharmacophore.
2. On 25 April 2003 there was a teleconference to discuss the computational chemistry, and in particular the strategy for both exploiting existing AFFITs, for example by adding functionality to them, and locating new AFFITs. (It should be noted that, where I use defined terms from the Agreement in this section of the judgment, I do so because that is how the term was used at the time.)
3. On 30 April and 1 May 2003 there was a meeting to discuss chemistry strategy and tactics. It was agreed that the APs, ICs and benzimidazoles were high priority AFFITs, whereas other series were of lower priority. There was also discussion about the identification of new AFFITs.
4. *The "kick-off meeting"*. The collaboration commenced in earnest with a "kick-off" meeting at Astex's premises in Cambridge, England on 19-20 May 2003 which was attended by 18 Astex representatives (including Dr Murray and Dr Congreve) and 13 AstraZeneca representatives (including Dr Edwards, Mr Berg, Dr Kolmodin and Dr Aharony). The meeting included a JEC meeting on 20 May 2003, at which it was agreed that a patent application would be filed to protect the pharmacophore. This application was subsequently filed on 10 September 2003 with inventors from both AstraZeneca and Astex.
5. One of the presentations at the kick-off meeting set out the "Hit Identification Strategy" which explained that the next milestone for the project was "the identification of two Hit series to transition into the Lead Identification phase (MS2)", with that transition being anticipated for December 2003. To achieve that, three "phases for HI" were proposed, two of which were to run in parallel: a Pyramid Screening Phase (April-August 2003), an AFFIT Optimisation Phase which aimed to achieve an IC50 of <100 µM (April-August 2003) and a Hit Optimisation Phase which aimed to achieve an IC50 of < 10 µM (September-December 2003).
6. ***Overview of work from May 2003 to the end of March 2004***. The original plan had been for Astex to use its HTx platform to screen AstraZeneca's NMR library. The JEC soon decided, however, that Astex should instead focus on solving structures of hits identified by NMR, and of follow-up compounds based on them. Astex's main contribution then became their crystallography work, and Astex was able to crystallise examples from AstraZeneca's three main series in BACE. Once Astex had solved the structure of a binder in BACE, it would feed back the structures to AstraZeneca through the AstexViewer overlay page. Not all compounds sent to Astex could be crystallised in BACE, so some crystallisation work in endothiapepsin continued at Mölndal.
7. AstraZeneca's NMR screening continued at Mölndal, and by March 2004 more than 4000 compounds had been screened, of which 60 had been identified as primary hits and sent to Astex for crystallography.
8. In addition to the screening and crystallography work, both sides devoted resources to the synthesis of analogues of hits that had been identified. Thus the AstraZeneca Wilmington team had a total of six chemists doing synthetic chemistry throughout 2003, who investigated over 10 different fragment series. The parties initially concentrated their respective synthetic efforts on the series they had brought into the collaboration: the Wilmington team particularly on the ICs, Astex particularly on the APs. The chemistry focus for for the ICs consisted of scaffold modification as well as AFFIT Optimisation, while for the APs it was just AFFIT Optimisation. Astex's synthetic efforts continued until the end of March 2004. After March 2004, Astex continued to provide crystallography support.
9. At a **JEC meeting on 12 September 2003** it was agreed that Program Milestone 1 under the Agreement (identification of the first Hit) had been met, triggering the payment by AstraZeneca under Section 7.2(1) of the Agreement. It is not entirely clear from the documents what the basis for this was, but it appears that it was agreed that the ICs and APs, which had been undergoing AFFIT Optimisation, were suitable for Hit Optimisation and thus should be selected as Hits. The most potent compounds in each series at that stage were AT5083, an AP with a BIACore IC50 of 168 µM, and M818616, an IC with a BIACore IC50 of 16 µM.
10. *ICs and APs*. Following the appreciation of the significance of the amidine motif, the ICs were given greater priority by Wilmington. By the end of 2003 a potency of <10 µM had been achieved. This was assisted by a suggestion made by Astex during a teleconference on 7 August 2003. Astex presented work it had done with the APs on two substituents designed to extend the molecule into the S1-S3 pockets, a napthyl group and meta-biphenyl rings in what came to be regarded as the B and C positions, and suggested that Wilmington considered making the corresponding ICs. The latter substituent, and variants of it, were incorporated into the ICs (and later series).
11. At a **JEC meeting on 4 February 2004**, it was agreed that the ICs met the requirements for one of the series for the MS2 transition to Lead Identification, but nevertheless it was not agreed that Program Milestone 2 had been met until selectivity screens had been completed. It appears that this was done shortly afterwards, because on 11 March 2004 AstraZeneca informed Astex that the payment under Section 7.2(2) of the Agreement had been authorised.
12. The APs ceased to be a focus due to discrepancies in potency measurements between AstraZeneca and Astex. After Astex stopped its synthetic efforts, the decision was made to concentrate on the ICs and DIHIs (see below). Progress with the ICs was intended to be translated to the APs, since they bind identically. When further improvements to the ICs did not materialise, however, progress on the APs similarly suffered.
13. *DIHIs*. A new series of hits called the dihydroisocytosine (DIHI) series arose from database mining at Wilmington in March 2003. The structure of the DIHIs is shown below.



1. The first DIHI was selected for screening from AstraZeneca's compound library by 17 March 2003 based on a search carried out by a Wilmington scientist, Dr Jeff Albert, for amidine-like compounds. (This was before Astex presented their hit series to AstraZeneca.) It was identified as active by July 2003, and was sent to Astex for crystallisation. Astex reported its structure in BACE in September 2003. Meanwhile Dr Albert's team in Wilmington had synthesized two additional DIHIs, one of which was more active than its parent with a potency of 189 µM. In January 2004 the DIHIs were identified as a high priority series, and Dr Edwards' group started synthetic efforts.
2. The DIHI series was progressed from an initial potency of 500 µM (compound reference M81863) to 7 µM (compound reference AZ12266492) within seven compounds, then to 0.5 µM potency (compound reference AZ12304146, which had B-C phenyl rings with a 3-methoxy substitution on the C ring) in a total of 17 compounds. The series made the MS2 transition from Hit Identification to Lead Identification in April 2004, and was looking promising for the MS3 progression to Lead Optimisation when the project started to transfer to Södertälje in late 2004. However, some hERG issues had been encountered.
3. On 2 December 2004 Dr Edwards gave a presentation at a meeting in connection with the transfer of the BACE project from Wilmington to Södertälje. A slide from this presentation summarises information about the top-performing seven DIHIs in cell assays. Some of these had B-C rings, and some did not. In an AstraZeneca presentation from 27 January 2005, 10 DIHIs were said to have a potency of <500 nM, of which the two most potent (compound references AZ12335870 and AZ12356703) had phenyl B-C rings joined to the core by a two-carbon linker and a 3-methoxy substitution on the C ring.
4. On 4 February 2005 Mr Berg gave a presentation, also in connection with the transfer, which included a slide summarising what was known about the SAR of the DIHIs. This indicated that the most potent DIHI had a chlorine substitution on the B ring and 3-methoxy substitution on the C ring (although other slides in the presentation showed that greater potency was achieved without the chlorine substitution). The presentation also showed that the DIHIs, including several with biaryl B-C rings, had some good DMPK (Drug Metabolism and PharmcoKinetics) properties, but some problems including poor efflux and/or poor brain/plasma ratios. At that stage, Södertälje's plan was to establish an SPR for hERG activity and compare it with the SAR for potency with a view to making a stop/go recommendation. A number of other series were also under consideration for exploration, including the DHIZs (see below).
5. The DIHI series was considered to be a completely different series to the ICs and the APs, with a much superior scaffold in terms of pharmacology and DMPK. Although the DIHIs had an sp3 (tetrahedral) carbon atom, and so (unlike the ICs and APs) they could have accommodated an A ring at the same time as B-C rings, no DIHIs with an A ring were made.
6. *Bicyclic DIHIs*. On 11 June 2004 Dr Murray, Dr Congreve and others at Astex had a brainstorming session to come up with ideas to modify the DIHI scaffold into a new chemical series that would not carry the same risks going forward into lead optimisation. Dr Congreve recorded a considerable number of ideas in his notebook. On 24 June 2004 the Astex team presented some of these ideas to the Wilmington team during a telephone conference with the assistance of a slide presentation. The principal suggestion they made was to incorporate a fused aromatic ring to replace the amide group, noting that related compounds were known from the literature and might be available to AstraZeneca from another programme. Another suggestion was to "consider 5 and 7 membered rings to alter ring strain", but no such rings were illustrated in the Astex slides. Astex subsequently supported the principal suggestion with some modelling work which indicated that the fused compounds should bind in a similar manner to the DIHIs. Frederik Edfelt of AstraZeneca had suggested exploring these compounds in April 2004, but at that stage the idea was not pursued because the connection was not made with the DIHIs.
7. Astex's principal suggestion led to the development by Wilmington by December 2004 of the bicyclic DIHIs (also known as dihydroisoquinolines or "DHIQs"). The structure of this series is shown below. Astex performed some crystallography on some examples which confirmed that the bicyclic DIHIs bound in the same orientation as the DIHIs, although at that stage they lacked potency. Bicyclic DIHIs synthesised by Wilmington in early 2005 showed promising potency.



1. *DHIZs (AIMs)*. Another new series of hits known at Wilmington as the aminoimidazolone ("AIM") series and at Mölndal as the dihydroimidazolone ("DHIZ") series was discovered through NMR fragment screening efforts by the SCL at Mölndal. The structure of the DHIZs is shown below.



1. The first two compounds tested in the series came from AstraZeneca's corporate collection, as opposed to being synthesized for the BACE project. The first (compound reference number M008915), was selected based on the same search at Wilmington that identified the first DIHI (see paragraph 168 above). It was tested by BIACore and identified as active in April 2003. The second (M008988) was identified from a search based on the first, and was identified as active in BIACore in August 2003. The difference between the two was that M008988 had a phenyl A ring, whereas M008915 had a methyl group in that position.
2. The DHIZ series was continuously evaluated by Wilmington and Mölndal as interesting in the remainder of 2003 and throughout 2004. AstraZeneca's work initially used further compounds from the existing AstraZeneca compound library, including a further six analogues identified for NMR screening by December 2003 from similarity searches.
3. By November 2004 Wilmington had started synthesis of new DHIZ compounds. Dr Edwards' evidence was that the first synthesised compound was AZ12385524. This compound incorporated an N-methyl group on the core. Dr Kolmodin gave evidence that she had suggested making this compound on a visit to Wilmington in April 2004 because she knew from the work that AstraZeneca had done on the ICs and DIHIs that this methylation had a positive effect on activity (which she rationalised as being due to prevention of protonation of the nitrogen). Dr Edwards explained that this had been discovered prior to the collaboration with Astex (see paragraph 80 above). Like M008988, AZ12385524 had a phenyl A ring. AZ12385524 was found to have a potency of 3 µM by BIACore. (As counsel for Astex pointed out in opening, AstraZeneca's pleaded case is that the first synthesised DHIZ was AZ12380417 which differed in having a single substituent at the chiral centre, a phenyl ring with a two-carbon linker, and a potency of 403 µM. Despite having pointed this discrepancy out, counsel for Astex did not attempt to resolve it in his cross-examination of Dr Edwards, no doubt because it does not matter.)
4. Astex unsuccessfully attempted to crystallise the first two compounds (from the compound library), but in December 2004 it successfully crystallised AZ12385524.
5. By December 2004, the DHIZ series was considered a high priority. In a presentation at a JEC meeting attended by Dr Angst and Dr Murray among others on 13 December 2004, the DHIZ series was among a number listed under the heading "Scaffold Hopping – New Series". The minutes of the JEC meeting recorded that the JEC agreed that these series represented "news [sic] series" developed "using scaffold-hopping" (it is not entirely clear whether this referred to just the DHIQs and DHIZs or all five series listed in the slide, but this does not matter). There was also discussion of the importance of the BACE project to AstraZeneca, where it had been ascribed "must win" status, meaning that it was more highly resourced than some other projects. At this stage, the aim was to reach the MS3 transition to Lead Optimisation by the end of the second quarter of 2005. (I would add that, although a further JEC meeting was planned for May/June 2005, in fact the December 2004 meeting was the last meeting of the JEC.)
6. At a BACE project meeting in Wilmington two days later, optimism was expressed that the SAR from the DIHI series could be translated to the DHIZ series, which was because they shared the amidine motif and an sp3 carbon, and because the crystal structures showed that the A and B substituents were expected to remain in the same positions despite the change from a 6-membered to a 5-membered ring.
7. In January 2005 a potency of 97 nM was achieved with DHIZ AZ12406230, which had a phenyl A ring and biphenyl B-C rings with a 3-methoxy group on the C ring (this is the active enantiomer of compound 3 in Jeppsson, as to which see below). In Mr Berg's presentation on 4 February 2005 (see paragraph 171 above), a slide set out a plan to explore the DHIZs further when Wilmington phased out. The slide queried whether the SAR for the 3-methoxy C ring was transferable from the DIHIs and noted that the hERG status of the DHIZs was unknown. It also included a structure of an ISIN (as to which, see below) with the word "Allowed?", but there is no evidence to suggest that this led to anything at that stage.
8. On 5 February 2005 Dr Albert sent Dr Edwards an email attaching a short presentation which set out some recent results and ideas for future work. The first slide showed the effect on potency of various different substitutions of the DHIZ core, with AZ12406230 being the most potent compound. Slide 2 showed six proposed analogues of AZ12406230 with differing A rings, including a 3-methoxyphenyl A ring and a 4-methoxyphenyl A ring. The first of the methoxyphenyl compounds suggested by Dr Albert was registered in AstraZeneca's database of compounds on 14 February 2005, with the remainder of the compounds on this slide being registered by the end of March 2005.
9. Slide 5 showed five proposed analogues of AZ12385524 with differing A rings. Two had an aliphatic A ring, namely a cyclohexyl or cyclopentyl ring. Although the cyclopentyl compound, AZ12422032, was made on 14 March 2005, and found to have an equivalent potency of 1.4 µM, the idea of using an aliphatic A ring was not pursued at that stage because it was more difficult to synthesise aliphatic analogues with substituents than aromatic analogues.
10. Two of the proposed analogues on slide 5 had 3- and 4-pyridine A rings, and Dr Albert suggested that these might form a hydrogen bond with a water molecule associated with tyrosine 71 in the S'-sub pocket of BACE under what was referred to as the "flap". A 4-pyridyl DHIZ with biphenyl B-C rings and a 3-methoxy group on the C ring, AZ12461790, was registered on 17 June 2005 and found to have an IC50 of 91 nM (or 0.07 µM, according to method).
11. On 9 February 2005 Astex held an internal brainstorming meeting attended by Dr Murray, Dr Congreve, Dr Chessari and Dr Joe Patel "to generate ideas around the latest results (structures and HERG activity)". Dr Chessari recorded the ideas which the group came up with in manuscript in his notebook. They included some ideas for DHIZ A rings, such as the use of 4-O-alkoxy groups to target tryptophan 76 in the S'-sub pocket of BACE, the use of a 4-pyridine ring, and the use of 3-substitution with methyl, chloro, ethyl or methoxy to fill the pocket. (See further below for another idea recorded at the same time.) On 14 February 2005 Dr Congreve emailed a scanned copy of Dr Chessari's notebook pages to Dr Edwards. As discussed above, however, Dr Albert of AstraZeneca had already come up with some of the same ideas.
12. Further work by Wilmington to develop a robust SAR for this series meant that DHIZ was a leading series by May 2005. A number of DHIZs with substituted phenyl A rings had been registered by the end of March 2005. The last compound sent to Astex by Wilmington was the DHIZ AZ12429686, which had a potency of 40 nM, in April 2005. This compound is shown in a slide from a presentation by Dr Kolmodin dated 18 April 2005 which summarises the SAR which had been established for substituted phenyl A rings. The compound had a 4-methoxy group on the phenyl A-ring, and this had improved the potency as compared to certain other substituents that had been tried. Another slide in the same presentation describes AZ12406230 and AZ12429686 as "forerunners towards MS3".
13. By the time Wilmington stopped work on the DHIZ series in May 2005, a potency of 7 nM had been achieved with AZ1244164, which had a phenyl A ring, a phenyl B ring and a fluoro- and chloro-substituted phenyl C ring.
14. ***Transfer to Södertälje and winding up of collaborative work***. Within AstraZeneca, a portfolio reorganisation meant that Wilmington would no longer pursue neurology as a therapeutic area. Accordingly, the BACE project started to transfer from Wilmington to Södertälje in late 2004, with the transition complete in May 2005. During the period of transition, the Wilmington site continued to perform chemistry up until May 2005, focussing on the bicyclic DIHI and DHIZ series.
15. The new Project Leader at Södertälje was Mr Berg. Mr Berg read the Agreement once, but found it very complicated. He focussed on the science, and left the Agreement to his Business Development colleagues.
16. On 2 March 2005 Dr Edwards summarised the progress of the project in emails to Mr Berg. Of the series that had been pooled at the start of the collaboration:

i) despite efforts, the potency of the aminobenzimidazoles had not been significantly improved;

ii) the ICs and APs had similarly stalled for the reasons explained above;

iii) the isothioureas were the subject of theoretical concerns about stability, toxicity and potency, but were a possible avenue for further investigation; and

iv) the aminoquinolines and piperidines had not been a focus of the collaboration and it does not appear that they had progressed.

1. Of the series identified from around the start of the collaboration:

i) the DIHIs remained promising. Dr Edwards had been concerned that Södertälje would abandon them due to hERG issues that had been identified, but Mr Berg confirmed that his team was going to keep up the series;

ii) the DHIZs also looked worthwhile; and

iii) there were other hits from HTS and virtual screening campaigns, as well as high priority AFFITs such as morpholine and benzazepine series.

1. The collaboration fizzled out as the transition from Wilmington to Södertälje progressed, and crystallography was brought in-house at Mölndal. Although it was suggested to some of AstraZeneca's witnesses that there was a desire on the part of AstraZeneca, and in particular Södertälje, to cut Astex out of further work on the BACE project, I am not satisfied that any such desire was established. Astex had itself already expressed concern about an open-ended commitment to support the project until CD nomination a year before at the JEC meeting on 4 February 2004, and the minutes of the JEC meeting on 13 December 2004 recorded that Astex had only committed resourcing (of 1.25 FTE) until May 2005. For its part, Södertälje had less need for crystallography anyway until it had progressed further with synthetic chemistry and it appeared likely that the SCL could meet its needs. Thus it suited both parties to end the collaboration. The position is summarised in an email from Dr Murray to Mr Berg and a colleague dated 17 May 2005:

"… Up to now we've been supplying AZ with protein [i.e. BACE] and crystallography but the agreement covering these aspects under our collaboration recently expired and nobody's contacted us to tell us what you need. Can I take it that you want to draw this part of the collaboration to a close and have decided to try to get the protein production working in-house? If that's the case, then that's fine, and we understand why you might wish to do this …"

1. Astex's involvement in the project effectively ended in late April 2005, although it continued to provide some input for a couple of months after that. On 9 May 2005 Astex sent AstraZeneca via the AstexViewer overlay page crystal structures for five DHIZs, including AZ12429686, bound to BACE, showing that the 4-methoxy group in AZ12429686 formed a hydrogen bond with Trp76. Wilmington asked for some final structural input in May 2005 and the last X-ray structures were solved by Astex in June 2005.
2. Although the contractual process for winding up the collaboration should have happened at this point, including the preparation of the Schedule 3.1 list of compounds, it did not. It was only with the 2009 Agreement that the position was regularised, and an expiry date of the Collaboration Term on 20 April 2005 was formally agreed. AstraZeneca sent Astex six-monthly updates about the BACE project both before and after the 2009 Agreement.
3. On 20 May 2005 Dr Edwards sent Mr Berg some ideas from both Wilmington and Astex about DHIZ ring substitutions, arising from the crystal structure of the 4-methoxyphenyl DHIZ compound AZ12429686:

i) A document dated 13 May 2005 from Astex (the last set of ideas that Dr Edwards received from Astex) that noted the existence of a hydrogen bond with Trp76 and suggested various other 4-position substituents that might hydrogen-bond with Trp76, as well as ideas for hydrogen-bonding to the water molecule seen in the S' subpocket.

ii) A document dated 16 May 2005 from Dr Albert, which similarly noted the potential hydrogen bond with Trp76 in the crystal structure. He reported that this 4-methoxy compound had a higher affinity than the equivalent compound with a phenyl ring, while the 3-methoxy substitution was disfavoured. He also provided data on B-C ring substitutions, showing that 25 compounds with differing C ring substitutions out of 62 analysed had a higher affinity than the 3-methoxyphenyl DHIZ compound reference AZ12406230.

***The development of CD1***

1. *Publication of Schering-Plough's patent application*. No series had reached the Lead Optimisation stage by the time that Wilmington's involvement ceased in late May 2005, but the expectation was that this would happen soon. On 30 June 2005, however, a patent application from Schering-Plough was published, which covered both the DIHI and the DHIZ series. This was a major setback for AstraZeneca's BACE project. To make matters worse, Merck and Wyeth had also published core structures that covered additional hits that AZ had identified from its NMR screening.
2. This development prompted AstraZeneca to adopt several approaches in an effort to get around the obstacle posed by the Schering-Plough application, including the following:

i) One was to press on with existing series, trying to find and exploit holes in the scope of the Schering-Plough application, such as by the use of sulphur-containing side chains in the substituents, and establishing SAR for these substituents. This in the end led to failure.

ii) Dr Edwards' Lead Generation group at Wilmington was asked to find scaffolds outside the scope of the patent application. This aspect of the project therefore returned to Wilmington from autumn 2005 to July 2006, running in parallel with Södertälje's work. Wilmington's efforts led to the ISIN series, as described below. Ultimately, this led to CD1.

iii) Södertälje also engaged in an effort to find new series, in particular by means of a computational chemistry workshop that took place in September 2005. As explained below, one of the new scaffolds proposed was what became known as the AiZ core, but the proposal lay fallow for nearly three years until theoretical work in 2008 prompted synthetic efforts. This started a chain of work that led ultimately to CD2.

iv) Södertälje continued with further NMR and high-throughput screening approaches, which did not bear fruit.

1. *Work on the DHIZ series at Södertälje*. When Dr Karlström joined the project in mid-2005 as a member of the Lead Investigation team, she started working on the DHIZ series. Her evidence was that the series which had been transferred from Wilmington, including the DHIZ series, were still in the LI phase. The majority of the work she was involved in from 2005 to 2007 involved scoping the DHIZ series by exploring new A, B and C ring configurations. When she started, there were no particular A, B or C ring configurations that were favoured. At that time, they did not have enough knowledge of the SAR of the DHIZ series, and so had not determined any favoured substituents.
2. Following the publication of the Schering-Plough patent application, several people spent time analysing it in order to find substituents which fell outside the claims. Dr Kolmodin then assisted with structure-based design, including docking, to see if those substituents might be suitable for the DHIZ series.
3. In addition to the intellectual property ("IP") problems, there were other challenges with the DHIZ series from the outset of the work at Södertälje, namely (i) lack of brain efficacy *in vivo*, which was attributed to low permeability and high efflux, (ii) hERG affinity and (iii) CYP inhibition. It was difficult to improve these other properties without adversely affecting potency. Thus a slide in a presentation given by Mr Berg on 30 September 2005 shows that a DHIZ with the reference number AZ12431116 was proposed for *in vivo* assessment because it had better hERG figures than a DHIZ with the reference number AZ12461790 albeit slightly worse potency.
4. Despite these difficulties, the DHIZ series was deemed to have passed the MS3 transition (to Lead Optimisation) at an LGC meeting on 27 June 2006, relying particularly on sulfonate substituents as IP differentiators. Although AstraZeneca normally required three series for the MS3 transition (and two were required under the Agreement), the LGC approved Mr Berg's proposal to proceed with a single series. Dr Kolmodin explained that this was something of a political decision taken by the project leaders so that the project was seen to be progressing. The DHIZ series did not have good permeability and, although active in plasma, did not satisfy the MS3 criterion of *in vivo* CNS (Central Nervous System) activity. Partly for that reason, it was decided to pursue back-up Lead Identification and Hit Identification programs, the former focussed on the ISINs and THIPs (as to which, see below). As the LGC, which was chaired by Dr Angst, put it in the minutes of the meeting:

"A key concern for the frontrunner program [i.e. the DHIZ series] relates to the heavy reliance on the sulfonate substituents as IP-differentiators because of their potential reactivity. Thus, the team is encouraged to carefully monitor the safety of sulfonate-containing lead compounds that progress in LO and to develop further scaffold modifications that reduce the reliance on these substituents. The team is also encouraged to put strong emphasis on permeability issues and to develop an understanding on those factors that contribute to poor CNS penetration."

1. On 12 September 2006 Dr Vestlng (who was Associate Director Global Discovery Alliances CNS & Pain Control i.e. in Business Development) asked Mr Berg, with reference to the Agreement, whether there would be a CD announcement in 2007. Mr Berg replied the next day that "We are planning to deliver a CD1 at the end of 2007 even if it will be a challenge". It appears that he was expecting that CD1 would be a DHIZ compound, and thus linked with the collaboration work.
2. After the MS3 transition, the DHIZ series was worked on by a team of seven Lead Optimisation chemists led by Dr Karlström. By November 2006, however, it was not showing promising signs with respect to brain exposure and efficacy. The most potent DHIZ compound had to be stopped in March 2007 due to severe CYP problems, and was replaced by another as the frontrunner, although lack of brain effect continued to be a problem. There was, however, a reluctance to stop working on the series, since no other series was at the Lead Optimisation stage.
3. In September 2007 Dr Söderman joined the BACE project as acting Chemistry Project Leader while Dr Karlström was on maternity leave. The key objectives for the DHIZ series at this stage were to increase potency, increase permeability, decrease *in vivo* clearance and achieve a brain effect. By this time, however, many companies were focussing their BACE efforts on amidines, including MSD, Amgen, Lilly, Novartis, Eisai and Shionogi. Dr Söderman therefore designed various sulfonate, silyl and pentafluorosulfanyl analogues in order to navigate the IP issues. Work continued into 2008, but without success in solving the problems with the series, and in June 2008 Dr Söderman recommended the DHIZ series be closed.
4. Finally, in about July 2008, work on the DHIZ series was stopped due to the difficulties in achieving brain efficacy, efflux problems and numerous third party patent applications.
5. ***Identification of the ISIN series by Wilmington***. A significant step in the development of CD1 was the identification and exploration of a series of compounds which became known both as the bicyclic AIM series and as the amino-isoindole ("ISIN") series, the structure of which is shown below.



1. Another of the ideas recorded in Dr Chessari's notebook pages on 9 February 2005 and emailed by Dr Congreve to Dr Edwards on 14 February 2005 (see paragraph 186 above) was an ISIN structure, together with a similar structure containing a pyridine ring rather than a phenyl ring, accompanied by a manuscript note which appears to read "5 ring replacements". These suggestions were not accompanied by any reasoning or by any structural or computational support. Dr Edwards' unchallenged evidence was that, as a result, he did not consider them further, nor did he recall ever referring back to them or even sending them on to Mr Berg in Södertälje.
2. Following the publication of the Schering-Plough application, a discrete project was assigned to Wilmington. Dr Edwards was at first asked to engage in a lead optimisation approach, namely to look at optimising an existing bicyclic series that had been transferred to Södertälje (the fused-phenyl series). He considered the series lacked sufficient intrinsic potency, however. He therefore suggested, and Mr Berg agreed, that his team should take a lead generation approach and identify other, new bicyclic scaffolds. Dr Edwards had some hope that the SAR from the existing bicyclic series (principally the bicyclic DIHIs) might be applied to new bicyclic scaffolds, and this guided his initial selection from a set of possible scaffolds he worked up with Dr Sylvester and set out in an email dated 25 October 2005.
3. On 30 October 2005 Dr Edwards sent his team an email proposing a set of eight bicyclic scaffolds (in some cases, with variants) that he felt were "strong candidates" for initial exploration. Among them was a "Phenyl 'AIM'", a phenyl ring fused to a DHIZ core, that is to say, an ISIN. Dr Edwards' rationale for proposing this series was that this was a parallel change to that between the DIHI and bicyclic DIHI cores, which was a change known to retain activity. The corresponding change had not been tried for the DHIZ series, so he saw it as the top priority for their efforts to identify good new cores (he described it in his 30 October email as a "no brainer" and in his 25 October email as one of a few scaffolds that "scream out to be made"). This did not necessarily mean, however, that the change would result in a better, or even good, inhibitor. He knew the changes would produce an entirely new series which could result in profound differences in potency.
4. Dr Edwards' thinking can be seen from an email that he sent to two colleagues on 5 January 2006 reporting on a visit the Wilmington team had made to Södertälje (emphasis in the original):

*"*Our reasoning [for evaluating alternating scaffolds before trying to optimise any specific scaffold] is based on both our experience in BACE and the particular expertise the Wilmington group brings to the project. Our experience has taught us that each different scaffold has its own strengths and limitations, and in spite of apparent 'structural similarities' each scaffold represents a different series. We have also learned that each scaffold has a different intrinsic potency relative to other scaffolds. …. This leads to the inescapable conclusion that the best way to progress the bicyclic series is to identify those bicyclic scaffolds that have the best intrinsic potency and ***then*** optimize them. If this strategy is not followed, then the risk is high that we will focus on a sub-optimal scaffold that will not be capable of being optimized to the required MS3 potency level. This risk is high because to date we have performed virtually no scaffold evaluation in the bicyclic series. Furthermore, if we ended our scaffold exploration early and focused on optimization of current scaffolds, then the probability that bicyclic scaffold exploration could be efficiently re-initiated in the future is also low.

…

I made the recommendation [to Mr Berg] that since the best compound in the current fused-phenyl bicyclic scaffold was 500 nM that Sodertalje pick-up optimization of new scaffolds once we achieve potency of <500 nM.

…

I suggest that the **deliverables** for the Wilmington team for the first half of the year be along the following lines: *Synthesize and evaluate at least 5 different bicyclic scaffolds in the bicyclic AIM and DIHI series (5 total scaffolds). After evaluating the in vitro potency results, make the decision to continue scaffold exploration or focus on scaffold optimization…*."

1. This supports Dr Edwards' evidence that the Wilmington team did not view scaffold hopping from the DHIZs to the ISINs as a form of optimisation, but rather the identification of a new series which required exploratory work to assess its potential as a viable series for subsequent optimisation. (In this regard, it may be noted that the figure of 500 nM is a greater degree of potency than required for completion of HI in the Research Plan at Schedule 1.37 to the Agreement, but a lower degree than required for completion of LI.)
2. Similarly, Dr Karlström gave evidence that the creation of a new core usually involved changing the properties of a molecule quite fundamentally. Properties such as stability, lipophilicity, pKa and permeability could not be predicted (although Dr Kolmodin later did modelling work on pKa prediction which is discussed below). Compounds with the new core were therefore tested first in Hit and Lead Identification before moving them to Lead Optimisation. Thus AstraZeneca's work on the ISIN series (and on the AiZ series, as to which see below) started with Hit Identification and progressed to Lead Identification and then Lead Optimisation.
3. After computational assessment, seven cores, including the ISIN core, were identified as preferred series for synthetic resources. Dr Sylvester worked on synthesising ISINs from around November 2005 to the end of July 2006. After unsuccessful attempts, he managed to reproduce the synthesis from a literature reference on 16 January 2006. As a result, three ISIN compounds, AZ12562643, AZ12562658 and AZ12562662 were registered on 8 February 2006. The first two had hydroxy-substituted phenyl A and B rings (but no C ring), while the third had plain phenyl A and B rings (and no C ring).
4. By the end of March 2006, it had been agreed that Wilmington would focus on the ISINs for the remainder of the time that it was engaged on the project. The activity of the first ISINs had looked interesting enough that the team prioritised the application of SAR knowledge from previous series, such as the DIHIs, to this series.
5. By 19 April 2006 Dr Sylvester had succeeded in making, at low yield, the first fully-elaborated analogue, compound reference AZ12584853, with a 4-methoxyphenyl A ring and biphenyl B-C rings. Its affinity was reported by Södertälje on 3 May 2006 as being 6.96 on the pIC50 scale (a negative logarithmic scale like pKa or pH, i.e. 10-6.96 M = 110 x 10-9 M = 110 nM on the IC50 scale).
6. In May 2006 the ISIN series passed the MS2 transition. On 5 May 2006 Dr Christer Nordstedt (Vice President of the CNS and Pain Control Local Discovery Research Area at Södertälje) told his counterpart at Wilmington, Dr Frank Yocca, that Dr Edwards and Dr Sylvester had delivered "a highly potent BACE inhibitor from a new and IP-free series", and that the BACE team was confident that this would greatly enhance their chances of reaching MS3 soon.
7. Dr Sylvester then developed an improved synthesis route that enabled a diversity of analogues to be generated. By the end of Wilmington's involvement at the end of July 2006, Dr Sylvester had registered 29 ISINs. Four of these had sub 100 nM potency, all of which had a 4-methoxyphenyl A ring and varying B-C rings. The most potent was AZ12618283, with an IC50 of 55 nM, which had a 4-pyridyl A ring, a phenyl B ring and a 2F-substituted 3-pyridyl C ring (this is the racemate of compound 5 in Jeppsson).
8. ***The development of the ISINs, THIPs and substituted ISINs: August 2006 to June 2007***. Dr Holenz became involved at Södertälje in August 2006 as Chemistry Project Leader for BACE Lead Identification. His team initially focused on the ISINs and another series known as the tetrahydroimidazopyridines ("THIPs") that had been developed in Södertälje earlier that year, the structure of which is shown below.



1. Dr Holenz explained that his team's aim was to deliver the MS3 transition. They were not interested in relying on SAR or SPR transfer from other cores, but empirically determined the SAR and SPRs for each core and for each of the A, B and C rings.
2. From the start, both the ISINs and the THIPs had issues with hERG liability, metabolic stability, and permeability (cell and CNS). Balancing these factors with good potency was a struggle, since an improvement in one aspect tended to worsen one of the others. It proved very difficult to improve the intrinsic liabilities of the ISIN and THIP series due to the high pKa of the amidine group.
3. On 12 September 2006 the Lead Identification team had a brainstorming session to find a way of avoiding the intrinsic liabilities of the ISIN and THIP series. Both Dr Holenz and Dr Rakos, who was a synthetic chemist on the lead identification team, independently came up with the idea of fluorine substitution of the ISIN core to shield the amidine warhead and to reduce its pKa. In particular, various ideas were presented by Dr Rakos for reducing basicity by attaching electron-withdrawing groups to the core or by exchanging carbon for nitrogen, principally with the aim of improving permeability. One of these ideas was fluorination. On 18 September 2006 Dr Rakos elaborated on this proposal with ideas for synthesis.
4. Dr Holenz viewed this as a lead generation activity that had the potential to create a new series. Making fluoro-ISINs was not part of exploring the ISIN series, since it would change the stereoelectronic properties of the core and require re-investigation of the A, B and C rings and the SAR/SPR for the new series.
5. A little later, on 6 October 2006, Dr Edwards sent Mr Berg an email after hearing at a meeting in Montreal that there might be pharmacokinetic problems with the ISIN series in which he suggested "in case you have not already thought of it" that it should be possible to change the physical properties of the compounds without changing the potency by modifying the aromatic benzo ring, in particular by adding a fluorine, which should lower the pKa and might also increase potency. The email refers to a fluorination which Mr Berg's team had carried out before, but unfortunately it is not known what this refers to.
6. 5-F substitution was tried first, on account of availability of the starting material that would give substitution in this position. 5-F substitution was also expected to have a greater influence on pKa than 3-F substitution. The first members of the 5-F-ISIN series or sub-series were synthesised in late 2006 and early 2007 by Dr Rakos. They did not show significant improvements in terms of hERG activity or permeability in the Caco-2 assay, however. In addition, the chemistry to deliver these compounds was extremely demanding, with low yield, so that Dr Rakos had problems synthesising the first representatives.
7. A further patent-related setback occurred in December 2006, with the publication of another Schering-Plough application, which was considered to cover almost everything in the ISIN series and most of the THIP series except for a particular group of macrocycles. This caused a re-assessment of priorities, and prompted a pause in synthetic work on the ISINs in early 2007. During the hiatus, the ISINs suffered another setback when an improved hERG assay showed the most permeable compounds to have worse hERG issues than had been thought.
8. In February 2007 the Neuroscience Research Management Committee made a provisional decision to continue work on the THIP and ISIN series, based on a way forward proposed by Dr Holenz after analysis of the patent application. Dr Holenz's view, both in light of the patent constraints and the need to improve CNS permeability, was that more drastic changes were needed, so the focus moved to altering the cores of both series although other work continued. In addition to the 5-F-ISINs, work was started around this time on a series or sub-series referred to as the aza-ISINs which had a nitrogen atom in the 6-membered ring (initially these were 3-aza-ISINs, and later 5- and 6-aza-ISINs as well). Some work had already been done on two other series or sub-series referred as to the cyano-ISINs and the chloro-ISINs.
9. On 1 March 2007 Dr Holenz and Mr Berg gave a presentation to the senior management team setting out proposals for achieving MS3 for both the ISINs and the THIPs by the then target date of May 2007. The main issue with the ISINs was identified as being to control hERG, with secondary issues including CYP liability, improvement of permeability and reducing pKa. By this time Dr Kolmodin was working on modelling the pKa of such compounds so as to enable better predictions to be made of the effects of changes on pKa (this work is described in more detail below). Work had been done on the effect of A-ring, B-ring and C-ring substitutions on pKa, and work was starting on the effect of modifications to the core, such as aza-ISINs. Thus some of the slides for each series showed "Future Potential Target Molecules", which included one slide in each case showing various "CORE Modifications".
10. Dr Holenz's evidence was that this scaffold hopping was classic lead generation activity to render a novel series which would have to be evaluated with regard to the different properties to deliver the lead identification criteria and hence the MS3 transition. The intrinsic properties of the new cores were not predictable (and indeed were intended to differ considerably by lowering the pKa), and the SAR and SPR were different for each series. It was not easy to predict the effects that alteration of the core would have, and none of the initial modifications showed significant improvements in brain penetration.
11. The aza-ISINs were synthetically extremely demanding, with a different synthetic approach having to be developed for each position of the nitrogen. Dr Rakos succeeded, however, in synthesising aza-ISINs that showed slight improvements in the permeability assay, and from March 2007 work on this series included selecting substituents on the A and C rings to reduce hERG activity.
12. Work also continued on the ISINs, with the synthesis of the active enantiomer of AZ12618283, AZ12766036, which was registered on 12 March 2007 and found to have a potency of 20 nM (this is compound 5 in Jeppsson).
13. A presentation by Dr Holenz and Dr Kolmodin and others to a management committee on 19 April 2007 reviewed the status of the ISIN and THIP series (both Lead Identification series) and the DHIZ series (the only Lead Optimisation series). The leading compound in the ISIN series at this stage was AZ12618283, which had demonstrated satisfactory brain exposure and brain effect in mice in a single experiment, but its pKa was too high. Work on reducing the pKa was reported, including data on an aza-ISIN version of AZ12618283, AZ12770431. This was calculated to have a reduced pKa, and had been found to have better permeability, but lower potency. It appeared that achieving satisfactory permeability was going to be easier with the ISINs and substituted ISINs than with the THIPs, but hERG liability was more of an issue with the ISINs.
14. Alternative approaches to reducing the pKa of the ISIN core included altering it with chloro- or cyano- groups on the phenyl ring, which was explored in May 2007. 5-F-ISIN synthesis also continued from spring 2007. However, many of the cores that were designed were too difficult to make.
15. Dr Holenz and his team designed and synthesized more than 180 compounds in the THIP, ISIN and ISIN-related series from August 2006 until June 2007. By June 2007, the focus had consolidated around the newly-made and planned aza-ISINs, bis-aza-ISINs, cyano- and hybrid cyano/aza-ISINs, in order to provide examples for patent applications before this space was also occupied by competitors.
16. *From June 2007 to March 2008*. In June 2007 Dr Holenz's team stopped working on BACE, and the 5-F-ISIN and aza-ISIN series were transferred to a team led by Mr Berg and Dr Britt-Marie Swahn. Their chemists had problems with the syntheses, and had to be coached by Dr Rakos. By this stage, efforts on the THIP series had decreased, since it was thought that the limits had been reached of what could be achieved with that series.
17. Since the 5-F-ISINs made by Dr Rakos around the end of 2006 had not been particularly promising, modifications other than fluorination had been investigated in the interim, and it was only in 2008 that fluorination was picked up again. In early 2008 attention turned to the 3-F modification. Dr Kolmodin was concerned that a 3-F group would result in poor binding, but Dr Swahn believed that it would engage in an intramolecular hydrogen bond to one of the nitrogen atoms in the amidine group, thereby shielding it as well as enhancing permeability. The shielding effect had also previously been proposed by Dr Rakos.
18. The first 3-F-ISIN, AZ12977798, which had a 4-pyridine A ring and phenyl-pyrimidine B-C rings, was synthesised by one of Dr Söderman's chemists and registered on 4 February 2008. The active enantiomer of that compound, AZ13032000, was registered on 28 March 2008 (this is compound 6 in Jeppsson). This was found to have a potency of 93 nM, but more importantly a lower pKa, increased permeability and brain activity. Indeed, AZ13032000 was the first compound in the BACE project to demonstrate a (dose-dependent) reduction of Aß in the brains of mice. From this, the team learned that the electron-withdrawing effect of the fluorine, coupled with the shielding effect of the fluorine on the exocyclic amino group, was essential for reducing the pKa and hERG, making the molecule more permeable and in turn more active. It was a welcome surprise that the 3-F substitution had a much more positive effect than the 5-F substitution.
19. *March 2008 to December 2009*. Following the first synthesis in March 2008, a number of 3-F-ISINs were synthesised and tested.
20. On 9 June 2008 the then Project Leader, Dr Johanna Lindquist (later Fälting), prepared a proposal, and on 12 June 2008 she gave a presentation to the LGT supporting the proposal, for the ISINs and THIPs to pass the MS3 transition to Lead Optimisation. In these documents the 3-F-ISINs were treated as part of the ISIN series. Two ISINs (AZ12766036 and AZ12971254) and one 3-F-ISIN (AZ13032000) were highlighted. In the case of the ISINs, optimisation was planned to concentrate on improving efflux, CYP and hERG liability.
21. On 30 June 2008 compound AZ13088924, a 3-F-ISIN with a 3-CF3- substituted 4-pyridyl A ring, a 3-F substituted phenyl B ring and a pyrimidyl C ring, was registered. On 7 August 2008 the active enantiomer of this compound was registered, AZ13107371 (this is compound 7 in Jeppsson). A presentation dated 20 August 2008 recorded that it had a pIC50 of 6.7 (IC50 93 nM) and a high permeability of 35 in the Caco-2 assay. By 3 November 2008 this compound had been found to have brain activity in mice and was regarded as the "BACE LO frontrunner".
22. Although 3-fluorination was a significant step forwards, the success of the 3-F-ISINs was far from assured, so lead generation efforts continued in an attempt to create back-up series. In 2008 the Lead Generation team was tasked with producing non-amidine containing cores, to try to overcome the efflux and permeability problems with the amidine-related compounds. Over 100 non-amidine compounds were synthesised in the six months to November 2008, but none of them proved potent.
23. In autumn 2008 Dr Karlström returned from maternity leave and began working on lead optimisation of the ISIN-related series. This involved changes to the core and to substituents, seeking to increase potency, reduce efflux and reduce hERG inhibition. Amongst the changes investigated were reducing steric bulk in the A ring, moving away from an aromatic C ring, and introducing polar groups at various sites. As part of this work, compound AZ13211205 was registered on 26 January 2009. This was a 3-F ISIN with a 3-CHF2- substituted 4-pyridine A ring, a phenyl B ring and a pyrimidyl C ring which was discovered to have lower hERG activity. This compound was the racemate of what became AZD3839 (i.e. CD1).
24. On 14 April 2009 two ISIN-related compounds (together with a single AiZ compound, as to which see later) were shortlisted for the MS4 transition:

i) AZ13213971, a member of the di-aza-ISIN series; and

ii) AZ13211205.

1. Work on AZ13213971 was stopped in August 2009 due to toxicity. The active enantiomer of AZ13211205, AZ13246373 (which had been registered on 15 April 2009), was selected for the MS4 transition as AZD3839 on 21 December 2009. It passed rat and dog toxicology studies in August 2010 and MS5 on 30 August 2010. **On 14 September 2010 Dr Farmery (who was then the Business Development Director at Södertälje) sent Dr Jeremy Carmichael of Astex an email (copied to Dr Fälting and Mr Renblad) informing him that a first CD had been nominated, and accordingly the Program Milestone 3 payment of US$1 million pursuant to Section 7.2(3) of the Agreement was due. Mr Renblad duly authorised the payment shortly afterwards**.
2. **CD1 was entered into a Phase I trial in July 2011**. At about the same time, on 4 July 2011, Dr Farmery sent Dr Carmichael an email (copied to Dr Fälting and others) informing him that CD1 had received Investigational New Drug (IND) approval from the US Food and Drug Administration, and accordingly the Development Milestone 1 payment of US$1 million pursuant to Section 7.3(1) of the Agreement was due. The payment was duly made shortly afterwards. Subsequently, however, the Phase I trial was stopped due to hERG issues. In January 2012 the decision was taken, with the involvement of Dr Budd (who was at that time Vice President of Translational Sciences of Neuroscience iMed in Södertälje), to stop all further work on CD1. Astex was informed about this by Dr Fälting on 4 April 2012. At the same time, Dr Fälting informed Astex that nomination of a second CD was anticipated for 10 April 2012.
3. ***The components of CD1***. The sources of the component parts of CD1 can be summarised as follows:

i) The core is a 3-F-ISIN core. The ISIN core was conceived by Dr Edwards in late October 2005, when he had the idea of adding a phenyl ring fused to the DHIZ core to create a new scaffold (see paragraphs 209-213 above). Subsequently Dr Holenz, Dr Rakos and Dr Edwards all had the idea of adding a fluorine substituent to reduce the pKa of the compounds in September and October 2005 (see paragraphs 222-224 above). 5-F substitution was tried first, in late 2006 (see paragraph 225 above). The first 3-F-ISIN was synthesised in February 2008 (see paragraph 237 above).

ii) The A ring is a 4-pyridine ring substituted at the 3- position with a difluoromethyl group. A 4-pyridyl A ring was proposed as a substitution for the DHIZ core by Dr Albert on 5 February 2005 (see paragraph 185 above), and the first 4-pyridyl DHIZ was registered on 17 June 2015 (see paragraph 185 above). A 4-pyridyl A ring was present in the ISIN AZ12618283 by the end of July 2006 (see paragraph 218 above) and in the 3-F-ISIN AZ13032000 by 28 March 2008 (see paragraph 274 above). The difluoromethyl substituent was not introduced until 26 January 2009 (see paragraph 242 above).

iii) The B and C rings are a phenyl ring and a pyrimidine ring respectively. These rings were present in AZ132032000 (see paragraph 237 above), although a fluorine substituent on the B ring was subsequently introduced and then removed. Astex drew attention to the fact that the same ring structure was present in an AP registered on 17 February 2004, but in that compound it was not attached to the core, or a chiral centre, but, via a methylene linker, to an exocyclic nitrogen. There is nothing to suggest that the B and C rings in CD1 derived from that source.

***The development of CD2***

1. *The computational chemistry workshop in September 2005*. The development of CD2 can be traced back to the computational chemistry (CMC) workshop in September 2005 mentioned above, and in particular the work done by Ms Viklund at this workshop. Such workshops were a regular annual event in Södertälje. The participants at this workshop included Dr Kolmodin, Ms Viklund and Mr Berg. It ran for the week of 12 to 16 September 2005.
2. As counsel for AstraZeneca pointed out, Ms Viklund was in a rather unusual position at the time of the workshop in a number of respects:

i) She had no chemistry degree, still less a PhD.

ii) She was a relatively junior computational chemist, having started with AstraZeneca in 2002 after her degree. She had experience of using AstexViewer in this capacity.

iii) She had no training in medicinal chemistry, but she had acquired some knowledge of this subject through her computational chemistry work. In particular, she understood that ligands and proteins often interacted via hydrogen bonds and she understood the importance of the shape of the ligand.

iv) She had little knowledge of the nomenclature of organic molecules, and in particular heterocyclic compounds (ones containing ring atoms such as nitrogen in addition to carbon).

v) She had little understanding of synthetic chemistry.

vi) She had no background in BACE. The workshop was her first and only involvement in the project until she returned to it much later, in 2008. (She did, however, know about the existence of the project, probably as a result of sharing a car to work with Dr Kolmodin at that time.)

vii) She nevertheless appears to have been quite creative, and to have been adept at thinking in 3D.

1. On the first day of the workshop, Dr Kolmodin, who had only recently returned to work from maternity leave, together with Dr Sven Hellberg (Head of Computational Chemistry), gave an introductory presentation. The presentation first explained the biological background, the structure of BACE, the rationale for developing an aspartyl protease inhibitor. The presentation then identified the three main series which had been developed: the ICs, DIHIs and DHIZs, showing how the potency of each series had been improved (in the case of the DHIZs, to 91 nM with AZ12461790), which it was explained all embodied the novel amidine pharmacophore. The 3D binding of the amidine motif (as well as the way the B and C rings fitted into the S1 and S3 pockets) was illustrated by reference to the DIHI AZ12335870 ("5870") (see paragraph 170 above). Although it is not mentioned in the slides, Ms Viklund's evidence was that the participants were informed that this was the most potent compound at that stage, with an IC50 of 80 nM.
2. It was then explained in a slide headed "Patent problems" that Schering-Plough had published a patent application covering the two main series and that Wyeth had found the same binding motif. In subsequent slides a number of "Backup plans" were identified, one of which was "Completely new core structures from CMC workshop".
3. The attendees were then instructed that by the end of the week they should each "present 3 novel core structures that you confidently believe bind to BACE" which should be exemplified with "a small number of molecules". This slide also mentions "An instruction on preferred R-groups and subsites to be reached", which referred to the substituents which were to be attached to their core structures and how they fitted within the pockets at the active site of BACE.
4. Another slide explained that the aim was to create "libraries" of compounds with IC50 below 5 µM, having a core which "should be outside our historical and current chemistry programs", with an asterisked footnote reading "Isocytosines, dihydroisocytosines, bicyclic versions, dihydroimidazalones, piperidines", and not covered by the Schering-Plough patent or any other BACE patent. The attendees could "use information from known hits (NMR, X-ray)", but if so "the core should be innovatively expanded/modified". Synthetic feasibility should be considered. Mr Berg's evidence, which is supported by the slides, was that it was explained to the participants that the core structures had to be new in order to be IP-free and patentable by AstraZeneca.
5. One of the slides sets out a list of tools which could be used as follows:
6. Dr Kolmodin and Ms Viklund confirmed that, as this suggests, all the structures provided by Astex via the overlay page were available to the participants. The last update to the overlay page with the final structures solved by Astex (see paragraph 194 above) had been provided by Astex on 20 June 2005. Dr Murray's unchallenged evidence was that the final version contained 171 structures including four structures not determined by Astex and three structures not in a complex. (It should be noted, however, that the structures in the overlay page were all 3D structures and not 2D structural diagrams.) Ms Viklund's evidence was that she had looked at many of these structures, but understandably she could not remember how many.
7. Another slide listed some "Representative BACE structures in AstexViewer" (i.e. in the overlay page). These included two DHIZs (AZ12380417 and AZ12406230) and three DIHIs (5870, AZ12338437 and AZ12300739). It is therefore likely that Ms Viklund looked at the 3D structures of at least these compounds bound to BACE in the overlay page.
8. It is not known what the "list of identified NMR hits" was. In any event, Ms Viklund did not recollect looking at such a list. As for "literature", Ms Viklund recalled looking at various types of aspartyl protease inhibitors being worked on by AZ's competitors (Merck's BACE inhibitor, Roche's renin inhibitor and an HIV protease inhibitor).
9. Ms Viklund gave a clear and largely convincing explanation of her design process, which I would summarise as follows:

i) Her objective, in accordance with the instructions given to the participants at the workshop, was to create novel cores.

ii) She looked at the available crystal structures in the overlay page using AstexViewer, and in particular the structure of the active site in BACE with its two catalytic aspartates, as well as the other available information.

iii) She found the number and diversity of the structures available in the overlay page rather overwhelming. She appreciated, however, that the general theme of the existing structures was that they interacted with the catalytic aspartates by hydrogen bonds. Accordingly, she concentrated on designing structures which could form hydrogen bonds with the aspartates. She knew that the principal hydrogen bond donor atoms were N, O and S, that N and O were generally preferred to S and that N generally formed stronger bonds than O.

iv) She designed her cores using a second computer, which was running a software product called Maestro. This is a tool which enables the user first to build chemical structures and then to predict their binding to a protein such as BACE (i.e. docking). In each case, the process she adopted was to start with two hydrogen bond donor atoms, usually two nitrogens, but sometimes a nitrogen and an oxygen, and then to build a core around them that would enable those atoms to form hydrogen bonds to the aspartates. Some of her cores had an amidine-like motif, but some did not.

v) In building a core around the two hydrogen bond donor atoms, she generally chose to incorporate them into five- or six- membered heterocylic rings, but she also designed some ureas with the donor atoms not in a ring. In some cases she made her cores into bicyclic systems.

vi) She docked cores that she thought looked reasonable, and she saved ones that looked as though they would bind to the catalytic aspartates. In carrying out this part of the process, she qualitatively compared the predicted binding of each core to BACE with the binding of 5870, because that was the most potent of AstraZeneca's inhibitors at that time.

vii) After saving a core, she then added substituent groups to that core which she thought would enable the compound to interact with the pockets in the active site. Her main preferred substituent group was an ethyl linked biphenyl methoxy group which formed part of 5870 (i.e. a two-carbon linker, a phenyl B ring and a 3-methoxy-substituted C ring). She also made frequent use of a methyl group, which is the other substituent attached to the chiral centre in 5870. (It appears that she understood that the core should preferably have an sp3 carbon so as to orient these groups correctly.) She checked the docking of the complete structure against 5870, and if it appeared to bind and to fit in the pockets she saved it. At this stage, she only saved one or two complete structures for each core.

viii) She recorded the designs she saved in an Excel spreadsheet which she created on the second day of the workshop, 13 September 2005, and last modified a week later, on 21 September 2005. As this indicates, the spreadsheet was a working document that was modified over time. Partly for this reason, and partly because it was evidently intended as a personal note rather to be presented to others, the spreadsheet in its final form is a rather confusing document which is not easy to interpret.

ix) When she first recorded her designs, she gave each one a random label (usually a letter/number combination). Subsequently, they were given different labels as explained below.

x) Despite the instruction to consider synthetic feasibility, she did not do so because she did not have enough knowledge in that area.

xi) She worked in what she described as "quite a disorganised fashion".

1. Ms Viklund initially produced structures based on at least nine new core ideas. One of these was a core which subsequently came to be known as the amino-2H-imidazlone or "AiZ" core. The structure of the AiZ core is shown below.



1. Ms Viklund's evidence was that she had not derived the AiZ core from any of the DHIZ or DIHI compounds. She described her creation of her core structures as "*de novo* design", which to her meant the process of collecting everything known and creating something new from that knowledge. Astex contends, however, that the documentary evidence demonstrates that she did derive the AiZ core from the DHIZ series. I shall return to this point below.
2. Dr Kolmodin's evidence was that she did not assist Ms Viklund to create any of her designs, although she was likely to have helped Ms Viklund with the docking protocol. Dr Kolmodin was available to answer questions, but did not recall sitting down directly to guide any of the participants. She did do some design work herself (on aminothiazoles), but she found it hard to distance herself from what she knew about the existing compounds.
3. When Ms Viklund presented her cores on the last day of the workshop, 16 September 2005, some of her colleagues (particularly Dr Didier Rotticci, who had experience of synthetic chemistry) immediately recognised that many of them were structurally unstable and difficult to synthesize, and were amused that she had paid so little attention to synthetic feasibility.
4. At some point, either towards the end of that week or early the following week, Dr Kolmodin assisted Ms Viklund to group her ideas into clusters. Although neither Ms Viklund nor Dr Kolmodin had a positive recollection of this, both witnesses thought it was likely that, as part of this exercise, Dr Kolmodin devised descriptive names for the various structures, which Ms Viklund used to replace the random labels in her spreadsheet. The structure which exemplified the AiZ core was labelled "imidazolone-like4". As this suggests, a number of similar structures were also given "imidazalone-like" labels. Both Ms Viklund and Dr Kolmodin thought that Dr Kolmodin had come up with this label because Dr Kolmodin had spotted that the "imidazalone-like" cores were structurally similar to, but different from, the DHIZ core. Thus the AiZ core has an additional nitrogen in the 5-membered ring, and it is not accurate to describe the AiZ core (unlike the DHIZ core) as an "-one", because it does not include a carbonyl (C=O) group. By contrast, Ms Viklund would not have been familiar with the term "imidazalone".
5. Perhaps at the same time, it is evident that Dr Kolmodin made some comments to Ms Viklund about some of her designs, because Ms Viklund recorded them in her spreadsheet. At some point Ms Viklund also recorded some comments made by Dr Rotticci. Some of these comments led to Ms Viklund discarding some of her proposals.
6. On 20 September 2005 Ms Viklund had a meeting with Dr Hellberg and Dr Jeremy Burrows (Chemistry Project Leader). In the course of that meeting, they came up with variations on some of Ms Viklund's original ideas, bringing the total number of proposed structures to 33. On 21 September 2005 Ms Viklund sent Dr Hellberg, Dr Burrows and Dr Kolmodin an email attaching a presentation listing these structures. The presentation is entitled "Five scaffold ideas from CMC workship, JV", although in fact it sets out six groups of structures labelled "Aminopyridin3", "Imidazolone-like", "Urea", "Aminothiazole", "Aminopyridin2" and "Cykliserad aminopyridin". In each case Ms Viklund's original ideas are shown in a yellow box. The slide presenting the "Imidazolone-like" scaffolds showed the AiZ core with a number of suggested potential substituents at the sp3 carbon, including two phenyl groups. It also showed a number of variants on the 5-membered ring theme. At least by this point in time, if not before, Ms Viklund had done crude calculations of pKa values for each of these structures using an online prediction tool called ACD, but she noted that more sophisticated quantum mechanical calculations of pKa still needed to be done. In the case of the AiZ core, the predicted pKa was 7.3, which was in the desired range of 7 - 7.5. (Such pKa values are also recorded in the spreadsheet.)
7. On 21 September 2005 Dr Burrows replied with comments on each group of structures. He said that the aminopyridine3 series was his favourite. Although the imidazolones looked OK, he preferred "a close analogue which has the amide in the ring" which he included a drawing of. Although Dr Burrows did not say so, this core is very similar to a DHIZ core. He suspected that the ureas were "dead". The aminothiazoles tied in nicely with ideas that he and Dr Kolmodin had coming out of NMR screening. The aminopyridin2s were "cool", but he had some concerns. The cyclised aminopyridines looked much less attractive. Dr Burrows finished by thanking Ms Viklund for all her "excellent" ideas.
8. On 22 September 2005 Ms Viklund replied thanking Dr Burrows for his comments and saying that "Your amide-version of the imidazalones looks good!". Like Dr Burrows, she did not mention the resemblance of his proposed core to the DHIZ core.
9. On 30 September 2005 Dr Kolmodin sent Mr Berg a presentation summarising 10 ideas for "new scaffolds" from the workshop obtained by means of "Pharmacophore searches", "'Manual' scaffold hopping and design", "Modification of known actives" and "Dockings". Four of these scaffolds, including "Imidazalone like" (AiZ), were credited to Ms Viklund and one to Ms Viklund and Dr Kolmodin jointly. The "Imidazolone like" slide describes it as a "new scaffold" (which is not the case for some of the others), and is annotated with comments (apparently from Mr Berg) that Dr Kolmodin should do further docking studies, and if satisfactory make three to five analogues, and that searches of the Marpat database should be undertaken (similar annotations appear on most of the other slides).
10. Shortly after this, however, Ms Viklund was told that none of her cores was to be taken any further because of the difficulty of synthesising them. Ms Viklund's core ideas therefore lay dormant and could easily have been forgotten. The ideas were not lost, however, because Dr Kolmodin kept a file containing the data for the workshop proposals – from Ms Viklund and others – on her computer. This proved to be of importance much later.
11. Returning to the question of the derivation of the AiZ core, Astex relies upon a number of points as showing that (i) many of Ms Viklund's ideas were derived from earlier structures in the project and (ii) in the specific case of the AiZ core, this was derived from the DHIZ series. I do not propose further to lengthen this judgment by going through all of these points (which occupy no less than 14 out of 52 pages of Astex's written closing submissions), and AstraZeneca's answers to them, in detail. AstraZeneca has never suggested that Ms Viklund was engaged in a "clean room" exercise designed to forestall the possibility of derivation. In any event, I accept that the documentary evidence clearly shows that Ms Viklund was inspired, to a greater or lesser extent, by the earlier structures which were available to her, in particular via the overlay page. Moreover, I think that Ms Viklund herself accepted that this was possible.
12. I do not accept that, considered as a whole, the evidence establishes that, as Astex contends, Ms Viklund was engaged in a process of systematic modification starting from those earlier structures. She did engage, with the assistance of Dr Burrows and Dr Kolmodin, in a process of systematic elaboration of her own ideas, but that was after she had come up with those ideas. When coming up with the ideas, however, I accept Ms Viklund's evidence that she tried to come up with new cores in the way in which she described. It is not surprising that she nevertheless came up with ideas which were similar to previous ideas given the nature of the instructions given to the participants in the workshop, which placed certain limits on the scope for originality, even though there were in theory many other possibilities. It is also not surprising that some of her own ideas amounted to variations upon certain themes. But as AstraZeneca points out, in the case of some of her ideas, there is little persuasive evidence of a link to earlier structures. I shall give an example of this in paragraph 274 below.
13. In the specific case of the AiZ core, Astex understandably places strong reliance on three pages of Ms Viklund's spreadsheet in its final form which have columns headed "origin of idea" that contain the entry "original series imidazolones" against the "imidazolone-like4" structure. The first page, headed "Docked", has a distinctly confusing layout. "Imidazolone-like4" appears in two places. On the first occasion, it appears in a column headed "chemistry" while "guanidinelik4a" appears in the same row in a column headed "docked". The entry in the "origin of idea" column for "original series imidazolones" appears to be referable to both structures, but the suggestion does not fit the one labelled "guanidinelik4a". On the second occasion, "imidazolone-like4" appears in the column headed "docked" and there is no entry in this row in the column headed "origin of idea". The second and third pages do not suffer from this problem, and clearly give "original series imidazolones" as "origin of idea" for "imidazolone-like4". Consistently with this, the other "imidazolone-like" compounds are said (at least on one reading of the first page) to have the same "origin of idea".
14. The evidence of Ms Viklund and Dr Kolmodin was that, although they did not positively recollect it, they thought it was likely that it was Dr Kolmodin who was responsible for these "origin of idea" statements (although they would have been typed up by Ms Viklund) and that the statements reflected the structural similarity of the "imidazolone-like" compounds to the DHIZ series. There are also two other reasons for treating these statements with a degree of caution. The first is that in some cases the "origin of idea" is given as "astexviewer", which begs the question of why a different "origin of idea" should have been ascribed to the "imidazolone-like" structures when there were DHIZ compounds in AstexViewer (i.e. the overlay page). The second is that in some cases the "origin of idea" is given as "NMR hit". Leaving aside the points that it is not known what list of NMR hits were available to the participants, and that Ms Viklund did not recollect seeing any such list, this invites the question as to why, and on what basis, Ms Viklund would choose to work from a NMR hit for which no structural information was available in the overlay page. On the other hand, Dr Kolmodin would have been in a position to recognise similarities between Ms Viklund's ideas and NMR hits known to Dr Kolmodin. This interpretation is supported by some entries in a column headed "Karins comments" which state "similar NMR-hit exists".
15. Another point which Astex relies strongly upon is the presence in all of the "imidazalone-like" compounds of a methyl substituent at the same position in the ring as the N-methyl group in the post-November 2004 DHIZ compounds (see paragraph 178 above). Astex contends that there was no *a priori* rationale for this, but points out that the slide in the presentation given on the first day of the workshop showing the improvements in potency which had been achieved in the ICs, DIHIs and DHIZs (see paragraph 249 above) demonstrated the increase in potency which had been achieved by an N-methyl group in that position in the DHIZs. But the slide also suggested that an N-methyl group in that position had a beneficial effect in all three series (albeit that the data presented were only sufficient to draw this conclusion unequivocally in relation to the DHIZs). As discussed above, it was Dr Kolmodin who had suggested N-methylating the DHIZs as result of what had been learnt from the ICs and DIHIs. Her rationale for making that suggestion in April 2004 would not have applied to the "imidazalone-like" compounds devised by Ms Viklund with carbon atoms at the relevant point in the ring, but there is no suggestion that the rationale was discussed in the CMC workshop. In those circumstances, it would not be surprising if Ms Viklund simply registered the beneficial presence of a methyl group in that position. As Astex points out, Ms Viklund had difficulty in explaining in her evidence why she had elected to use a methyl group there, but it would not be surprising if she had forgotten this detail 12 years later even assuming she had been conscious of the reason in the first place.
16. As for Ms Viklund's other ideas, in one case Astex relies on the fact that a core labelled "aminothiazol\_b\_no\_carb" is the same as that of a compound to be found in Schedule 3.1 to the 2009 Agreement which Astex suggests may have been an NMR hit; but there is no evidence that it was an NMR hit, let alone that it was on a list of NMR hits available to participants in the workshop. It is also unlikely, given her instructions, that Ms Viklund would have simply copied an existing core. Furthermore, the label suggests that this was (or was recognised to be) a variant of another of Ms Viklund's cores labelled "aminothiazol\_b", from which "aminothiazol\_b\_no\_carb" differs in lacking a carbonyl group, but there is no "origin of idea" for "aminothiazol\_b\_no\_carb" whereas the "origin of idea" of "aminothiazol\_b" is stated (at least on one reading of the first page) to be "astexviewer" and the "Karins comment" against "aminothiazol\_b" is "similar NMR-hit exists". Thus the document suggests that Ms Viklund first came up with "aminothiazol\_b", which Dr Kolmodin recognised as similar to an NMR hit, and then produced "aminothiazol\_b\_no\_carb".
17. Overall, the conclusion I draw is that Ms Viklund was inspired by the DHIZ series in coming up with the AiZ core, as she was with the other "imidazalone-like" cores, and in that sense Dr Kolmodin's comments recorded in the spreadsheet as to the "origin of idea" were accurate. I am not persuaded, however, that Ms Viklund designed the AiZ core by consciously starting with a DHIZ core and then modifying it. Still less did she design the AiZ core, or a structure exemplifying it, by starting with a specific DHIZ compound and then modifying that. On the contrary, as discussed above, her choice of substituents was strongly influenced by 5870, a DIHI.
18. *Dr Kolmodin's pKa model*. After the CMC workshop, work continued on the DIHI and DHIZ series, the THIP series was developed by Södertälje and the ISIN series was developed by Wilmington as discussed above.
19. In January 2007 Dr Kolmodin returned from a second period of maternity leave. At that time, Södertälje was trying to reduce the pKa of compounds to improve permeability and to reduce hERG activity (which was a particular problem for the ISIN series), but reducing the pKa had to be balanced against loss of potency. Dr Kolmodin inherited a project from Dr Rotticci, who had been developing a model to produce improved pKa predictions using quantum mechanical calculations (the predictions produced by ACD were inaccurate for complex molecules such as those involved in the BACE project). Dr Kolmodin updated and refined this model over a period of over a year using experimentally determined pKas. By the end of 2007 she was predicting the pKa of a host of molecules from different series with reasonable accuracy.
20. In about late November 2007 Dr Kolmodin looked at several ideas for new cores that she had in her records from the CMC workshop and other ideas that had come up during the project. Many of the team members designed or drew different amidine-containing 5-membered rings and 6-membered rings, both bicyclic and monocyclic. They were put through Dr Kolmodin's model, which she used to identify potentially good new novel cores. Some of the new cores she was trying in the model are shown in a presentation by Dr Kolmodin dated 4 December 2007, along with modifications to existing cores such as DHIZ and ISIN. One of the new cores, labelled "Chemistry 3", was Ms Viklund's AiZ idea from the CMC workshop. Dr Kolmodin added two phenyl A and B rings for the purposes of the calculation, and calculated that the resulting compound had a pKa of 6.96.
21. Although Dr Kolmodin agreed in cross-examination that "the core this particular analogue or proposed analogue was modifying was the DHIZ core", in context she cannot have meant that that was the derivation of the core, but rather that it was an attempt to move away from the DHIZ core. In any event, as she made clear, she did not design the AiZ core and did not herself know how Ms Viklund did.
22. In early 2008 Dr Kolmodin started work on a Free-Wilson analysis that allowed separation of pKas into contributions from component parts of molecules in order to speed up calculations, quickly obtain the pKa of cores, and obtain information about how different A, B and C rings could affect the pKa of the cores.
23. In around May 2008, Dr Kolmodin was looking at ways to try to reduce the hERG affinity of the new 3-F-ISINs, in particular by avoiding cores with an aromatic element and by shielding the amidine. Amongst the ideas she considered were Ms Viklund's cores, and she concluded that the AiZ core had potential for a number of reasons, including the fact that it was IP-free and that the predicted pKa was in the desired range. She prepared a presentation dated 19 May 2008 setting out her thinking which set out some proposals for decreasing aromaticity and shielding the amidine. Among both sets of proposals were two AiZ compounds with phenyl A and B rings, one with a fluoromethyl substitution, and the other with a methoxymethyl substitution, of the core (rather than the methyl group which had been proposed by Ms Viklund).
24. On 20 May 2008 Dr Kolmodin sent the Lead Optimisation synthetic chemistry team an email asking for comments, and in particular synthesis routes, for the partly-elaborated core shown below.



1. In the email Dr Kolmodin explained:

"It would be nice to put an 'amidine shielding' functionality at R, for instance F-methyl or C-O-C, in analogy with the ISIN modifications. Or R could be extending outwards towards the S2 or S2' pockets in the enzyme.

The A and B ring should be some common BACE rings to start with.

The core has a calculated pKa of 7 when R is methyl."

1. At that stage, this proposal was not pursued, however, probably because the synthetic chemists were too busy working on the existing series.
2. What prompted more interest was a model that Dr Kolmodin developed later in 2008. In February/March that year, she had noticed from her pKa calculations and from developments in the F-ISIN and aza-ISIN series that permeability was not correlating simply with pKa. She hypothesised that other factors were also important, and thought of using solvation energy as a way of assessing lipophilicity. She developed this idea further, and in September 2008 she studied the pKa, solvation energy and permeability differences in around ten different ISIN cores and some THIP and DHIZ cores. She drew scatter plots of pKa against solvation energy, and noticed that there was a section of the plot – which she later termed the "window of success" – that contained cores with good permeability.
3. Dr Kolmodin added theoretical new cores into the scatter plot using calculated pKa values. These cores included the AiZ core, with methyl, trifluoromethyl and phenyl substituents at the R position. Dr Kolmodin noticed that, although the methyl-AiZ core fell outside the "window of success", it was close to it, and both the pKa and the solvation energy were very close to that of the core with the best potency to hERG ratio at the time (the F-aza-ISIN series). She concluded that it looked promising.
4. Dr Kolmodin then applied a variety of models to predict a range of properties (which included lipophilicity, solubility and hERG) of novel cores based on a virtual library of compounds generated by appending known A, B and C rings to the cores. Dr Kolmodin's evidence was that this was a rational approach because the vectors of the tetrahedral carbon in the AiZ core were similar to other vectors that had been looked at for other compounds in the project and therefore using known A, B and C rings gave one an approximate idea of what was going to happen. This work confirmed her earlier view that the AiZ core was better than the ISIN core from a hERG perspective because it had a good combination of pKa and solvation energy leading to good permeability. Furthermore, the lipophilicity of the AiZs was predicted to be lower than that of the ISINs, which was an advantage because it gave greater scope for optimisation. In addition, the AiZ core was more IP-free and offered the possibility of shielding the amidine.
5. When explaining her thinking at this point in paragraph 103(e) of her first witness statement, Dr Kolmodin added that "since the aromatic-ring of the ISIN-core did not interact with the BACE protein (rather it acted as a scaffold to modify the physicochemical properties), it could be sacrificed as long as the remaining core had the right properties." In context, this was clearly not a statement about the derivation of the AiZ core, but about Dr Kolmodin's reasons for thinking that the AiZ core looked promising, and might represent an improvement on the ISIN core.
6. In cross-examination counsel for Astex seized upon the word "sacrificed", and put it to Dr Kolmodin that she was "modifying the ISIN core … as a design step". Although Dr Kolmodin answered "yes" to this question, she immediately went on:

"The earlier phase in the project, we were doing these different substitutions on the ISIN core in order to understand the structure activity/property relationships that was needed to get the compound to enter into the brain."

In my judgment Dr Kolmodin (who gave evidence in English, which is not her mother tongue) was not intending to accept that the AiZ core was derived from the ISIN core, still less that she herself had modified the ISIN core to arrive at the AiZ core, but to explain further the point she had made in paragraph 103(e). Since Astex had not alleged that the AiZ core was a modification of the ISIN core, Dr Kolmodin had no reason to address her mind to that question. Moreover, as I have already observed, Dr Kolmodin's evidence was that she did not design the AiZ core, Ms Viklund did, and she herself did not know how Ms Viklund had designed the AiZ core.

1. In late September or early October 2008 Dr Kolmodin explained her results and reasoning to two of the chemists in the Lead Generation team. They were Ms Viklund and Dr Frederik Rahm. Ms Viklund had returned to work from maternity leave in January 2008, and at that point had been assigned by Dr Hellberg to the BACE project as a computational chemistry member of the Lead Generation team. Dr Rahm was leading the Lead Generation synthesis team. Dr Rahm and Ms Viklund reacted with enthusiasm. In the case of Ms Viklund, this was the first time she had been reminded of the work she had done at the CMC workshop three years before. Together with Dr Rahm's boss, Dr Ylva Gravenfors, they persuaded Mr Berg and Dr Fälting to devote synthetic resources to making AiZ compounds which could then be tested. Since the AiZs were a completely new series, they had to be explored, in the same way that other series had previously been explored, to see if they would be suitable for subsequent Lead Optimisation.
2. *Synthesis of AiZ compounds*. To begin with, only one synthetic chemist in the Lead Generation team, Dr Jan Blid, was assigned to this task. The AiZ compounds were little documented in the literature. Dr Blid developed a new synthesis, producing the first AiZ compound, AZ13154285, in low yield in early November 2008 (and winning the internal "Synthesis of the Month" award in December 2008). It turned out, however, that the compound was not active against BACE.
3. Dr Blid was then joined in his efforts by Dr Ginman, and together they faced some very challenging chemistry to synthesise a set of test compounds. The synthetic route they used involved a phenyl attached to the core at the R position shown in paragraph 282 above (referred to as R1 in some of the contemporaneous documents), and did not involve an A ring. The compounds were all found to be inactive.
4. Dr Ginman modified the strategy, which permitted other groups at the R position of the core. First, he tried an iso-propyl, and then, at the end of November 2008, a methyl. The methyl group was not only beneficial for synthesis, but was hoped to be beneficial for potency. The methyl compound, AZ13175482, was the first that was active enough to show the AiZ core was worth pursuing, with a FRET IC50 of 3.5 µM. It had a phenyl B ring and a 3-methoxy-phenyl C ring, but still no A ring (instead it had a methyl group in that position). In mid December 2008 the tenth AiZ was made, AZ13192482, at very low yield. This had an isopropyl R group, a 4-methoxy-phenyl A ring, a phenyl B ring and a 3-pyridine C ring. It had an IC50 of 2.1 µM.
5. The synthetic route still limited the possibilities, however, and did not allow the desired combination of a methyl on the core and an A ring, in particular a 4-methoxy-phenyl A ring. This required an innovative synthesis to be developed, which came to be known as the "Holy Grail" chemistry since it allowed flexible substitution at the R, A and B positions. Dr Ginman and Dr Blid shared the April 2009 Synthesis of the Month award for this achievement.
6. With this new synthetic route, the AiZ series was explored further to build the potency of the AiZ compounds. In general terms, it was found that the SAR of the A, B and C rings was mainly parallel between the ISIN series and the AiZ series, which was the hope. The SAR was not straightforwardly transferable, however: some structural elements could be transferred, others not. In particular, an A ring on an AiZ had quite a different effect than on an ISIN, since the ISINs are much more basic than the AiZs. Moreover, a 4-pyridine C ring was quite active in ISINs, but not in AiZ due to lowering of the pKa. In addition to potency, work was done on the other properties of the compounds. By March 2009 22 AiZ compounds had been made, with the most potent being the 22nd, AZ13230776, with an IC50 of 32 nM. That compound had a methyl group on the core, a di-methyl and 4-methoxy A ring, a phenyl B ring and a pyrimidyl C ring.
7. On 14 April 2009 Dr Fälting presented a proposal for the AiZ series to pass MS2 to the LGT. In the heading to her fourth slide she described the AiZ core as a "New Core Smilar [sic] to LO Series". Under the heading "Background" on the same slide she stated (among other things) "New core – not evaluated by LO". By this date, 31 AiZ compounds had been synthesised, seven of which were particularly highlighted in the sixth slide. The LGT, which was chaired by Dr Angst, approved the MS2 transition. The minutes of the LGT meeting on 14 and 15 April 2009 also described AiZ as a "new core not evaluated by LO".
8. At the same time, the single most potent AiZ, AZ13243578 (the active enantiomer of AZ13230776), which was registered in April 2009 and had a potency of 13 nM, was shortlisted for MS4, thereby bypassing Lead Optimisation (together with the di-aza-ISIN and 3-F-ISIN compounds mentioned in paragraph 243 above). It subsequently failed in November 2009 due to toxicity issues, however.
9. On 18 June 2009 Dr Fälting sent Astex an update on the BACE project in which she informed Astex that a new chemical series, the AiZ series, had been identified in Hit and Lead Identification and had passed MS2 on 14 April 2009. She went on to refer to AiZ as a "new core – scaffold hopping from LO series". In context, it is fairly clear that "LO series" refers to the DHIZ series.
10. In about September 2009 Dr Karlström came up with the idea of using a 5-propargyl substituted 3-pyridine C ring. An AiZ compound with a three-membered A ring, phenyl B ring and this C ring, AZ13306361, was synthesised, and found to have a potency of 78 nM. The success of the propargyl substituent was a surprise, but it was found to flip the C ring and fill the S3-subpocket, displacing the water molecule.
11. On 16 December 2009 Dr Fälting proposed that the AiZ series should pass the MS3 transition to Lead Optimisation. This proposal was approved by the LGT, which was chaired by Dr Angst, at a meeting on 16 and 17 December 2009. The MS3 decision recommended that the A and B-C rings should be a particular target for investigation during Lead Optimisation. The pyridine C ring was seen as a potential problem in terms of CYP inhibition.
12. *Introduction of a cyclohexyl A ring*. Whereas the SAR for the BACE enzyme assay potency was reasonably transferrable from earlier series to the AiZ series, this was not the case for cellular potency, *in vivo* potency or DMPK properties. Moreover, it was not possible to say that the SAR for the A, B and C-ring substituents would be transferrable across series as these substituents are core-specific to improve and balance the properties of the core and the molecule as a whole.
13. In early June 2009 Dr von Berg, Dr Swahn and Dr Karlström gave a presentation reviewing progress and future plans for the ISINs and AiZs. So far as the AiZs are concerned, this recorded among other things that:

i) for the A ring, while aryl SAR information from the ISIN series could be used, alkyls/cycloalkyls/heterocyclyl substituents needed to be scoped, in particular to see if the pKa of the core could be increased;

ii) for the B ring, alkyls, cycloalkyls and ethers had not been explored in the ISIN series due to IP limitations, so needed to be explored;

iii) in the C ring, while SAR for aromatic and hetero-aromatic rings was known from the ISINs, there were also plans to explore possibilities not known from previous series such as ethers, amides and alkyls; and

iv) the R position on the core was also to be the subject of scoping work, on the basis that it was considered to be important for shielding of amidine to avoid efflux (similar to the shielding effect of 3-F in the 3-F-ISINs), and that it afforded the possibility to affect hERG, CYP and selectivity.

1. In some respects, the AiZ core was notably worse than the F-ISIN core. In a "matched pair" comparison set out in a later presentation by Dr Kolmodin, it was shown that an AiZ (AZ13223238) had a cell-based activity 100-fold worse than an F-ISIN with the same substituents (AZ12997841) even though the FRET potency and the permeability of the AiZ compound was slightly better than that of the F-ISIN compound. The SAR was found to be less transferable in the cell-based assay, which had been used from the early days of the project along with the *in vitro* enzyme assay, but later in the project was found to correlate better with animal results.
2. While initial progress in Lead Optimisation was fast after the MS3 transition in December 2009, this did not continue for long. By November 2010 progress had been stagnant for some time. The AiZ series was nearly shut down at this point.
3. To save the series, Dr Kolmodin and the chemistry team generated new ideas using AZ13243578 as the starting point. The objective was to increase the cell potency by increasing the pKa of the core. Whereas the concern for the ISIN series and modified ISINs had been to reduce the pKa, the AiZ core had a much lower pKa to start with (around 5, as opposed to about 7 for 3-F-ISIN), so the pKa had to be raised. This was because compounds with pKa lower than around 6 lost potency in cell assays, which is related to the BACE enzyme being localised to acidic compartments.
4. This meant that electron-withdrawing substituents suitable for the ISIN series (such as aromatic A-rings) were not suitable for the AiZ series. On the other hand, greater IP freedom for the AiZ core meant that there was greater scope to explore different substituent groups. Dr Kolmodin employed a computational approach to search for possible alkyl groups as A-position substituents that were sterically suitable, that would make a hydrogen bond with Trp-76 and could optionally displace the water molecule in the S3 subpocket using software called Molecular Operating Environment (MOE). She searched more than 100,000 fragments, which yielded many hits. Matching groups were manually reviewed, including for their potential to increase pKa. Dr Kolmodin then docked the promising virtual compounds to check their anticipated binding.
5. The outcome was a set of substituents that included pyridones, which were known to be highly potent in earlier series. Also included were some substituted cyclohexyls, from which Dr Kolmodin proposed using a 4-methoxy substituted cyclohexyl (with optional additional 4-substitution). The 4-methoxy-cyclohexyl had been previously proposed for the ISIN series, but never made. A plain cyclohexyl group had also been tried as an electron-rich A ring to raise the pKa by Dr Ginman in about April or May 2009, but without success.
6. The 4-methoxy cyclohexyl compound, AZ13475426 (active enantiomer AZ13497910), was synthesised in mid December 2010. It was found to be more potent (140 nM, with the active enantiomer AZ13497910 having a potency of 33 nM), but this was still not potent enough, and it had problems with CYP3A4 inhibition. Again, the series came very close to being shut down.
7. *Spirofication*. What saved it this time was an idea from Dr Karlström to introduce a spirocyclic system to connect the A and B rings (see the structure of CD2 shown in paragraph 4 above). The hypothesis was that rigidifying the molecule into the bioactive conformation could increase potency, because of the entropic advantage of reducing the number of rotatable bonds in the ligand. Dr Karlström and Dr Kolmodin designed a series of compounds based on this idea, and modelling suggested that spirofication would result in a very potent compound, so a prophetic patent application was filed in December 2010. (The need to file the application at that particular time arose because of the imminent publication, in early January 2011, of another AiZ application from the group.) This spirofication step would not have been possible with an aromatic A-ring, since it could not make the two necessary bonds from a single carbon to the spiro ring.
8. The most promising compounds were selected for synthesis based on their predicted properties. In February 2011 the first active spiro-AiZ was synthesised, a racemate AZ13511133 that had 100-fold greater potency than the un-spirofied compound. AZ13534566 was the active enantiomer of this compound and had a potency of 0.6-0.8 nM, decreased hERG liability and no CYP3A4 inhibition. In May 2011 Dr Kolmodin and Dr Karlström were given "Design of the month" and "CNS & Pain iMed Star" awards for their work on the spirofication of AiZ.
9. The Lead Optimisation team worked on improving the spiro-AiZ series still further through 2011 and into 2012. None of the compounds ended up surpassing the early spiro-AiZ AZ13534566 – AstraZeneca was lucky that its first spiro-AiZ turned out to be the best. In November 2011 this was one of three compounds shortlisted for CD nomination.
10. Further optimisation work on back-up AiZ compounds was led by Dr Söderman. His team continued to optimise and design additional spiro-AiZ compounds with the aim of improving brain exposure, permeability and efflux. In the event, no compound was found that had a better profile than AZ13534566, which was selected as a candidate drug on 10 April 2012 as AZD3293. On 17 April 2012 Dr Farmery sent Dr Carmichael an email (copied to Dr Fälting and others) informing him that a CD2 had been selected, albeit without giving any details.
11. ***The components of CD2***. The sources of the component parts of CD2 can be summarised as follows:

i) The core is a spiro-AiZ core. The AiZ core was conceived by Ms Viklund at the CMC workshop in September 2005 (see paragraphs 247-275 above). It was then ignored for three years, before being resurrected by Dr Kolmodin in September 2008 as a result of her modelling work (see paragraphs 276-290 above). The idea for spirofication came from Dr Karlström in December 2010 (see paragraph 309 above).

ii) The A ring is a 4-methoxy cyclohexyl ring. This was proposed by Dr Kolmodin as a result of her MOE work (see paragraphs 305-308 above).

iii) The B ring is a phenyl B ring. This had been used in previous series, but not in spirofied form.

iv) The C ring is 4-propargyl substituted 3-pyridine ring. This was devised by Dr Karlström in September 2009 (see paragraph 299 above).

***Subsequent events***

1. *Jeppsson*. Jeppsson *et al*, "Discovery of AZD3839, a Potent and Selective BACE1 Inhibitor Clinical Candidate for the Treatment of Alzheimer Disease", *J. Bio. Chem.*, 287 (49), 41245-41257 (2012) ("Jeppsson") is a paper by a team of 14 authors from AstraZeneca, including Drs Karlström, Kolmodin and von Berg, and the Karolinska Institute. It was submitted for publication on 9 August 2012, submitted in revised form on 24 September 2012, published online on 9 October 2012 and published in print form on 30 November 2012. A paragraph headed "Discovery and Optimization of Amidine-containing BACE1 Inhibitors Leading to AZD3839" on page 41248 briefly describes a sequence of steps which is shown diagrammatically in Figure 1 on page 41249 captioned "Discovery and optimisation of amidine-containing BACE1 inhibitors leading to the *in vivo* compound AZD3839". I reproduce Figure 1 below.



1. Prior to trial, Astex relied upon Figure 1 and the accompanying text of Jeppsson as accurately setting out the evolution of AZD3839, i.e. CD1. Dr Karlström, who drew Figure 1, gave unchallenged evidence, however, that it was not intended to, and did not, accurately depict the derivation of CD1. Furthermore, during the trial, Astex accepted that the account is inaccurate in at least one respect (namely, in suggesting the ISINs were derived from the THIPs as the arrow from compound 4 to compound 5 might be taken to suggest). That being so, Jeppsson cannot be regarded as reliable evidence of the manner in which CD1 was developed. Rightly, it was not relied upon by Astex in its closing submissions.
2. ***Communications in relation to CD2***. When CD2 was selected as a candidate drug in April 2012, Dr Budd (who was on the iMed Leadership Team, which made the decision) did not recall there being any discussion as to whether there were any obligations owed by AstraZeneca to Astex.
3. In May 2012 Dr Budd informally, and in July 2012 Dr Budd formally, took over as the Global Project Lead for the BACE project from Dr Fälting.
4. At the beginning of July 2012 Dr Budd and the BACE project were transferred to a new "virtual" Neuroscience iMed unit based in Cambridge, Massachusetts. The unit was "virtual" because it did not have any internal laboratory resources. It was made of a small number of staff who worked with external companies to whom certain functions were outsourced. The Södertälje site was shut down in September 2012 with many of the employees being made redundant. (The Wilmington site had already been closed by September 2010.)
5. Up until this point, the only inkling that Dr Budd had about the genesis of CD2 came from a conversation with her husband, Dr Haeberlein, who was a computational chemist and the then Head of Medicinal Chemistry at Södertälje, when he had returned from a workshop on the BACE project in 2009 or 2010 excited about some major breakthroughs made by computational chemists at Södertälje which had led to a new chemistry direction being pursued and would generate prospective compounds. This was not something she had in mind in May 2012 when she took over the project, however.
6. On 18 June 2012 Dr Fälting sent Dr Budd a presentation by Dr Farmery about the Astex collaboration dated 20 April 2012, in which one slide said that "AZD3839 [CD1] and AZD13534566 [CD2] derived from starting points identified during active collaboration, all other series independent" and were "subject to ... development/commercial milestone payments and royalties".
7. On 25 June 2012 there was a handover meeting for the transfer of the BACE project from Södertälje to Cambridge which Dr Budd attended. At that meeting, Dr Farmery communicated his belief that CD1 and CD2 were subject to the Agreement, although without going into depth regarding his rationale for this view. One of his slides repeated the same statement about CD1 and CD2 from Dr Farmery's April presentation. The presentation contained a slide – albeit in a part of the presentation that was not in fact presented because there were no medicinal chemists on the receiving team – that had an arrow pointing from an amidine fragment with R groups on it to the DHIZ and 3-F-ISIN cores. This was Dr Söderman's slide, and he thought it was likely that the arrow was intended to mean that part of the DHIZ was similar to the amidine fragment, although he could not remember. This may have been the sense in which CD1 and CD2 were said to have been "derived" from starting points identified during the collaboration, i.e. that they shared the amidine motif. In any event, Ms Viklund was not at this meeting and nobody asked her for her input in respect of it.
8. Dr Budd understood from both Dr Farmery and Dr Fälting that CD2 was covered by the Agreement. Their reasons for this view are unknown. Ms Viklund did not know if she had ever explained to Dr Fälting how she had invented the AiZ core. Ms Viklund's evidence was that in 2009 Dr Fälting (who was a biologist) only cared about it being a new series.
9. Dr Budd proceeded initially on the basis that had been set out by Dr Farmery and Dr Fälting. She soon began to have doubts, however. By July 2012, she had recalled the brief conversation with her husband following the workshop in 2009 or 2010. Following her first review of the Agreement in August 2012, she further doubted whether CD2 fell within the scope of the Agreement.
10. On 22 November 2012 Dr Budd sent Dr Srinivasan an email saying she questioned whether CD2 really was within the scope of the collaboration with Astex. Dr Srinivasan had joined AstraZeneca in April 2012 as Head of the Business Development & Licensing team for the new Neuroscience iMed unit. He had understood from Dr Farmery in June 2012 that CD2 was a drug within the Agreement and so carried financial obligations.
11. Dr Budd's query was passed on to Mr Johnston, who had recently joined the iMed unit as Chief Counsel. Mr Johnston had some discussions about the issue at the start of 2013. During the course of these, he consulted Dr Holenz, who was clear in his view (albeit based only on his own second-hand knowledge) that Astex had made no contribution to the discovery and development of CD2, and who could not discern anything in Schedule 3.1 from which he, as a chemist, could deduce CD2. There was no need to reach a definitive conclusion at that point, however, not least because the next event that could trigger a payment would be entry into Phase II, which was still a long way off and might never happen, since CD2 was not then even in Phase I. It was therefore decided to maintain the status quo until resources had been deployed to do the appropriate due diligence and technical assessment to consider the point.
12. The period from 2012 to 2013 was very busy for the project, and the question of whether CD2 was a Collaboration Compound was not of immediate importance or relevance. Furthermore AstraZeneca did not want to initiate a conflict with Astex that might later turn out to have been entirely unnecessary if CD2 failed to progress. The status quo was therefore maintained.
13. Dr Budd and Mr Johnston had a conversation in January 2013 with Dr Mark Duggan, who was head of Medicinal Chemistry in Cambridge, Massachusetts, and with Dr Holenz, the conclusion of which was that it would require further work to investigate the derivation of the molecules against the history of the project. Dr Holenz's recollection was that he indicated that he had been hired in August 2006 and that other people would therefore know about the earlier period, but that his understanding was that Ms Viklund had invented the AiZ series at a brainstorming session.
14. Dr Duggan took the view that payment ought to be made, but Mr Johnston was not sure whether that was on the basis that it was or was not a Collaboration Compound. Mr Johnston understood Dr Duggan to have been reluctant to rock the boat: AstraZeneca Neuro was trying to build positive collaborations with third parties, and Dr Duggan was concerned with maintaining and managing relationships.
15. On **8 February 2013** Dr Budd and Dr Srinivasan sent Astex an update on the BACE project which stated that **"AZD3293 [CD2] was nominated April 2012** and is now the lead molecule" and that "No other 'Collaboration Compound' is currently under evaluation". As Dr Budd accepted, this implied that CD2 was a Collaboration Compound. Dr Budd explained that this was maintaining the status quo.
16. In November 2013 Dr Budd's group made a written submission to a joint meeting of the Early Stage Program Committee and the Late Stage Program Committee, which governed entrance into early and late stage clinical trials, respectively. This contained (at least in the drafts available) the statement that "**Astex Therapeutics know-how and capability played a significant role in the early phases of the BACE project and AZD3293 [CD2] originated from this platform**". This was in a section of the document provided by the IP department, and Dr Budd's evidence was that it was included because of the decision to maintain the status quo and that it reflected the view that had been communicated by Dr Farmery and Dr Fälting.
17. On 22 February 2014 Mr Johnston sent Dr Carmichael an email (copied to Dr Budd) introducing himself and attaching a six-monthly update on AZD3293 (CD2) dated 10 February 2014 which Dr Budd and he had prepared. Under the heading "Next development step in the BACE program", this stated "When AZ has determined that the Ph2 has become a Ph3, we will communicate that transition to Astex, and pay the Ph3 milestone". As Dr Budd accepted, this was a clear representation that CD2 was a Collaboration Compound. She explained that the necessary due diligence had still not been carried out to investigate the matter at that point. In response to the suggestion that the update should nevertheless have expressed doubts as to the status of CD2, Dr Budd said that she would only have communicated a change in AstraZeneca's position to Astex if it had been her job to do so (which it was not, being a decision above her pay grade) and if AstraZeneca had the evidence to support a new position (which it did not). Mr Johnston's evidence was that this update was a deliberate continuation of the position that Dr Farmery had earlier adopted.
18. In 2014 AstraZeneca began to look for potential partners on the project, and discussion began with Lilly. Lilly queried whether CD2 was covered by the Agreement, and formed the view that it was not. This was initially after having been provided with Schedule 3.1 and presumably having reviewed the patent for the chemical entity.
19. It was agreed between AstraZeneca and Lilly that Lilly would not contribute to payments to Astex unless a court determined that financial obligations were owed, in which case the costs would be split 50:50 between AstraZeneca and Lilly.
20. Once the deal with Lilly was closed in September 2014, and in light of the milestone payable on commencement of a Phase II/III clinical trial in December 2014, it became apparent to Mr Johnston that it was necessary to determine whether or not CD2 was a product covered by the Agreement.
21. Mr Johnston therefore had further discussions in October 2014, including with Dr von Berg, which did not reveal anything to support the suggestion that CD2 was covered by the Agreement. AstraZeneca's electronic laboratory books were retrieved at Lilly's request, and the first tranche was put together by 20 February 2015. By around that date AstraZeneca had concluded that CD2 was not a Collaboration Compound. Astex's demands for an update became more insistent as CD2 moved into Phase II/III, and so Mr Johnston informed Astex of AstraZeneca's change of position on 24 February 2015.
22. Mr Johnston was criticised in cross-examination both for not having expressed doubts in his communications with Astex as to whether CD2 was a Collaboration Compound before AstraZeneca had reviewed the position and reached a conclusion and for having communicated AstraZeneca's change of position to Astex in February 2015 without providing a full explanation for that change of position. In my view these criticisms are not only inconsistent, but equally unjustified. In any event, even if I were to take the view that AstraZeneca should have communicated its doubts sooner and should have provided a fuller explanation than it did when it changed its mind, that would not be relevant to any issue in the case.
23. Astex contends that (i) AstraZeneca has never had any real doubt that CD2 was a Collaboration Compound, (ii) AstraZeneca was only spurred to contend otherwise as a result of a hard bargain driven by Lilly and (iii) AstraZeneca is only defending this claim because of the potential financial consequences regardless of merit. In my judgment the evidence does not support any of these three propositions. In particular, it comes nowhere near justifying proposition (iii), which I would point out is an allegation of some seriousness.

**Is CD1 a Collaboration Compound?**

1. In order for CD1 to be a Collaboration Compound, it must have been "discovered or identified as a direct result of AFFIT Optimisation, Hit Optimisation or Lead Optimisation". I have considered the interpretation of this definition in paragraphs 120-146 above. For brevity, I shall use "discovered" to mean "discovered or identified" in the remainder of this judgment.
2. For the reasons given in paragraphs 89-112 above, I have concluded that, on the true construction of the Agreement, the Program ended when the Collaboration Term ended on 20 April 2005. I do not understand Astex to dispute that, if that is so, CD1 is not a Collaboration Compound because it was not discovered as a direct result of chemical structure modification "performed as part of the Program". It is necessary for me to consider, however, what the position would be if Astex were correct that the Program continued after the Collaboration Term.
3. My findings of fact as to how CD1 was developed are set out in paragraphs 197-246 above. In very brief overview, the principal stages of that development were as follows:

i) the development of the ISIN core;

ii) the development of the 5-F-ISIN core;

iii) the development of the 3-F-ISIN core; and

iv) the finalisation of the substituents, leading to CD1.

1. Astex's case in broad outline is that CD1 was discovered as a direct result of LO of ISIN Leads (in particular, AZ12766036 and/or AZ12971254 and/or AZ13032000) which were in turn discovered as a direct result of HO of ISIN, DHIZ and/or DIHI Hits which were in turn discovered as a direct result of AO of DHIZ, DIHI and/or AP/IC AFFITs. In its closing submissions Astex concentrated on the contentions that (i) the identification and development of the ISIN core from the DHIZ core was AO, alternatively HO, and (ii) the development of CD1 from earlier ISINs was LO.
2. AstraZeneca admits that CD1 was discovered as a result of optimisation of AZ13088924 (Compound 7 in Jeppsson) which in turn was discovered as a result of optimisation of AZ13032000 (Compound 6 in Jeppsson), **but denies that CD1 was discovered as a direct result of AO, HO or LO**. In broad terms, AstraZeneca takes two main points. First, AstraZeneca disputes that either (a) the development of the ISIN core or (b) the development of the 3-F-ISIN core amounted to AO, HO or LO. Secondly, AstraZeneca contends that the path by which CD1 was developed was both far too long and far too indirect for the discovery of CD1 to have been a direct result of AO, HO or LO starting from any compound discovered during the Collaboration Term. A more minor point relied upon by AstraZeneca is that the A ring did not derive from the collaboration.
3. There is no dispute that:

i) certain compounds within the DHIZ series which were synthesised during the Collaboration Term met the criteria for AFFITs;

ii) the development of certain compounds within the DHIZ series during the Collaboration Term amounted to AO; and

iii) at least one compound within the DHIZ series (AZ12385524) met the *in vitro* potency criterion for a Hit.

1. **In my judgment CD1 was not the direct result of AO, HO or LO for a number of reasons**.
2. First, although I accept Astex's point that the ISIN core can be regarded as having been discovered as a direct result of chemical structure modification of the DHIZ core, I do not consider that the identification and development of the ISIN core amounted to AO within the meaning of the Agreement. This is because it did not start from AFFITs, nor was the aim to generate optimised AFFIT structures that formed the bases for the identification of Hits. **By late October 2005** the DHIZ series, and certainly the leading members of that series, met the criteria for Hits (whether or not they had been formally selected or nominated as such pursuant to the Agreement), and AstraZeneca was in the advanced stages of (to use the terminology of the Research Plan) Lead Identification (with the transition to Lead Optimisation being deemed to have been achieved in **late June 2006**). Dr Edwards' aim in devising the ISIN core was to develop a new series which could form the basis for Lead Identification. (The fact that part of the objective was to develop an IP-free series I regard as neutral.)
3. Secondly, although it follows from what I have just said that Astex has a stronger case that the identification and development of the ISIN core amounted to HO, I am not satisfied that the development started "from a Hit". There are two aspects to this. First, the development did not start from any specific compound(s). Secondly, it did not start from any compound(s) which had been selected or nominated as (a) Hit(s) pursuant to the Agreement. In saying this, I should make it clear that I have not overlooked the fact that a number of DHIZs, including in particular AZ12406230 and AZ12429686, are listed in Schedule 3.1 to the 2009 Agreement.
4. Thirdly, even if the identification and development of the ISIN core did amount to HO, I do not consider that the development of the 5-F-ISINs, still less the 3-F-ISINs, amounted to LO. It does not matter for this purpose whether or not one regards the F-ISINs as distinct series to the ISINs, which is certainly a debatable point, although I lean in favour of AstraZeneca's contention that they are distinct. What matters was that the aim of Dr Holenz and Dr Rakos and their colleagues in devising the F-ISINs was again to develop compounds which could form the basis for Lead Identification, and in particular to lower their pKa and improve their permeability.
5. Fourthly, although it again follows from what I have just said that Astex has a stronger case that the identification and development of the F-ISINs amounted to HO, I am again not satisfied that the development started "from a Hit".
6. Fifthly, CD1 was not discovered as a result of LO of any ISINs which had been selected or nominated as Leads under the Agreement. In particular, neither AZ12766036, nor AZ12971254, nor AZ13032000, is listed in Schedule 3.1.
7. Sixthly, and in any event, I do not consider that CD1 was the direct result of any AO, HO or LO within the meaning of the Agreement. I agree with AstraZeneca that the path from anything that qualifies as AO, HO or LO to CD1 was too long and indirect for this.
8. Finally, I shall specifically address Astex's contention that AZ13032000 was selected as a Lead Compound in June 2008 (see paragraph 239 above), and that CD1 was a direct result of LO starting from that compound. I do not accept this. Although AZ13032000 was considered by AstraZeneca to be a candidate for LO, it was not selected or nominated by AstraZeneca as a Lead Compound pursuant to the Agreement (the Collaboration Term having ended three years beforehand). Moreover, in order to qualify as a Lead Compound, it would have to have been discovered through HO. If, on the other hand, AZ13032000 did qualify as a Lead Compound, then I incline to the view that CD1 was the direct result of LO starting from that compound.
9. On the other hand, I should say that I do not accept that the mere fact that the A ring was not identified during the Collaboration Term prevents CD1 from being a Collaboration Compound.

**Is CD2 a Collaboration Compound?**

1. Again, I do not understand Astex to dispute that, if the Program ended when the Collaboration Term ended on 20 April 2005 as I have concluded, CD2 is not a Collaboration Compound because it was not discovered as a direct result of chemical structure modification "performed as part of the Program". It is again necessary for me to consider, however, what the position would be if Astex were correct that the Program continued after the Collaboration Term.
2. My findings of fact as to how CD2 was developed are set out in paragraphs 247-313 above. In very brief overview, the principal stages of that development were as follows:

i) the design of the AiZ core;

ii) Dr Kolmodin's modelling work, which led to AiZ compounds being synthesised;

iii) the development of the spiro-AiZ core; and

iv) the finalisation of the substituents, which proceeded in parallel to spirofication, leading to CD2.

1. Astex's case in broad outline is that CD2 was discovered as a direct result of LO of AiZ Leads which were in turn discovered as a direct result of HO of AiZ Hits which were discovered as a direct result of AO of DHIZ AFFITs.
2. AstraZeneca denies that CD2 was discovered as a direct result of AO, HO or LO. Again, in broad terms, AstraZeneca takes two main points. First, AstraZeneca disputes that the development of the AiZ core amounted to AO, HO or LO. Secondly, AstraZeneca contends that the path by which CD2 was developed was both far too long and far too indirect for the discovery of CD2 to have been a direct result of AO, HO or LO starting from any compound discovered during the Collaboration Term. AstraZeneca also relies upon the fact that neither the A ring nor the propargyl-substituted C ring nor the spirofied core derived from the collaboration.
3. Again, the points noted in paragraph 343 above are not in dispute.
4. In my judgment CD2 was not the direct result of AO, HO or LO for a number of reasons.
5. First, I do not consider that the AiZ core was discovered as a direct result of chemical structure modification of the DHIZ core. Although Ms Viklund was inspired by the DHIZ core, she did not design the AiZ core by modifying the DHIZ core. Moreover, her proposal went nowhere until it was appreciated as a result of Dr Kolmodin's pKa modelling work that the AiZ core would be worth devoting synthetic resources to. As for Dr Kolmodin's work, that was important, but it did not amount to chemical structure modification. In any event, I do not consider that the identification and development of the AiZ core amounted to AO for similar reasons to those given in paragraph 345 above.
6. Secondly, although I consider that Astex has a better case that the identification and development of the AiZ core amounted to HO, I am not satisfied that the development started "from a Hit" for similar reasons to those given in paragraph 346 above.
7. Thirdly, CD2 was not discovered as a result of LO of any AiZs which had been selected or nominated as Leads under the Agreement. No AiZ is listed in Schedule 3.1.
8. Fourthly, and in any event, I do not consider that CD2 was the direct result of any AO, HO or LO within the meaning of the Agreement. I agree with AstraZeneca that the path from anything that qualifies as AO, HO or LO to CD2 was too long and indirect for this.
9. Finally, I shall specifically address Astex's contention that AZ13243578 was selected as a Lead Compound when the AiZ series passed the MS3 transition in December 2009 (see paragraph 300 above), and that CD2 was a direct result of LO starting from that compound. I do not accept this. AZ13243578 was not selected or nominated by AstraZeneca as a Lead Compound pursuant to the Agreement (the Collaboration Term having ended four and a half years beforehand). Nor did it have the status of a Lead Compound in December 2009, because it had failed due to toxicity issues the month before (see paragraph 297 above). Moreover, in order to qualify as a Lead Compound, it would have to have been discovered through HO. If, on the other hand, AZ13243578 did qualify as a Lead Compound, then I incline to the view that CD2 was the direct result of LO starting from that compound.
10. On the other hand, I should say that I do not accept that the mere fact that the A ring, the propargyl-substituted C ring and the spirofied core were not identified during the Collaboration Term prevents CD2 from being a Collaboration Compound.

**Astex's application to re-re-amend its Particulars of Claim**

1. Astex applied during closing submissions for permission to re-re-amend its Particulars of Claim to advance a new alternative case that CD2 was the direct result of LO in which AiZ compounds were discovered or identified as a result of chemical structure modification of the ISIN series. The new case is based on the evidence given by Dr Kolmodin in paragraph 103(e) of her first witness statement and during cross-examination (see paragraph 289 above). This application was opposed by AstraZeneca.
2. The relevant principles have been helpfully summarised by both Carr J in *Quah v Goldman Sachs International* [[2015] EWHC 759 (Comm)](http://www.bailii.org/ew/cases/EWHC/Comm/2015/759.html%22%20%5Co%20%22Link%20to%20BAILII%20version) at [38] and Coulson J in *CIP Properties (AIPT) Ltd v Galliford Try Infrastructure Ltd* [[2015] EWHC 1345 (TCC)](http://www.bailii.org/ew/cases/EWHC/TCC/2015/1345.html) at [19].
3. The relevant procedural background is as follows. Astex commenced these proceedings on 16 November 2015. Its case on CD2 as originally pleaded in its Particulars of Claim was based partly on AstraZeneca's representations prior to February 2015, partly on what little information was publicly available and partly on inference. It was inevitable that the case would have to be further particularised after disclosure by AstraZeneca. AstraZeneca did not in the end complete its disclosure until 14 October 2016.
4. On 8 November 2016 Chief Master Marsh ordered Astex to answer AstraZeneca's Third Request for Information, in particular so as to set out its case in relation to direct result of LO leading to CD2, by 13 January 2017. That time was subsequently extended to 20 January 2017, when Astex served its Response. In the meantime, AstraZeneca had served its witness statements in two tranches on 22 December 2016 and 10 January 2017. Dr Kolmodin's first witness statement was included in the second tranche. Thus Astex had had it for 10 days when it served its Response.
5. AstraZeneca was dissatisfied with Astex's Response and applied for an order requiring a further and better response. That application came before me on 15 February 2017. Shortly before the hearing Astex served a draft Amended Particulars of Claim in an effort to address AstraZeneca's concerns about the Response. AstraZeneca did not accept that the proposed amendments sufficed to make Astex's case clear. The upshot of the hearing was that Astex agreed to revise the proposed amendments to try better to address AstraZeneca's concerns by 1 March 2017. Astex duly served a revised draft, and AstraZeneca then consented to the amendments. As counsel for AstraZeneca pointed out, the Amended Particulars of Claim constituted Astex's third attempt to formulate its case on CD2, and in particular on CD2 being the direct result of LO, following both completion of disclosure and the service of Dr Kolmodin's first witness statement.
6. In its written opening submissions for trial Astex indicated its intention to seek permission to re-amend its Particulars of Claim, in particular to allege that CD2 was the direct result of HO or LO of AiZ compounds. After some debate during counsel's oral opening submissions, Astex slightly revised its proposed re-amendments and AstraZeneca consented to them. Accordingly, this was Astex's fourth attempt at stating its case on CD2 being the direct result of LO following completion of disclosure and service of Dr Kolmodin's first witness statement.
7. Dr Kolmodin gave evidence on day 5 and day 6 of the trial (10 and 11 May 2017). Astex first indicated its intention to apply to re-re-amend its Particulars of Claim in its written closing submissions exchanged at 2 pm on 23 May 2017, and first formulated the proposed amendments in draft Re-Re-Amended Particulars of Claim served on the evening of 24 May 2017, after counsel for AstraZeneca had completed his oral closing submissions.
8. Astex accepts that the amendment is a late one, but contends that it should be given permission to make the amendment because it would prejudice Astex not to be able to advance this alternative case and it would not prejudice AstraZeneca since the amendment arises out of evidence given by its own witness and no further evidence is required. AstraZeneca contends that the amendment is a very late one, that no sufficient explanation or justification for the lateness has been given by Astex, that AstraZeneca would be prejudiced because, if the amendment were to be permitted, it would wish to adduce further evidence from Dr Kolmodin, and that the new case is hopeless anyway.
9. In my judgment Dr Kolmodin's evidence, when properly analysed, does not support the proposition that the AiZ core was a modification of the ISIN core for the reasons explained in paragraph 288-289 above. It follows that there is no basis for the proposed amendment, and it should be refused for that reason. I shall nevertheless consider the position on the assumption that, contrary to my assessment, Dr Kolmodin's evidence provides a sufficient basis for the proposed amendment.
10. In my view, the amendment is properly characterised as a very late one. Given that the new case is based on Dr Kolmodin's evidence, Astex has given no satisfactory explanation or justification for not notifying AstraZeneca of the new case prior to its written closing submissions. If notice had been given earlier, it might well have been possible to re-call Dr Kolmodin. If the amendment is permitted now, then an adjournment of the trial would be necessary for that to happen. I do not accept the submission of counsel for Astex that there is no need to re-call Dr Kolmodin. Dr Kolmodin's witness statements were not directed to the case which Astex now seeks to advance, nor would she had had any inkling of it when answering questions in cross-examination. It would only be fair to AstraZeneca to permit the amendment on condition that it could serve a further witness statement from Dr Kolmodin upon which she could then be further cross-examined. Thus the choice is between permitting the amendment on that condition, which would necessitate an adjournment, and refusing the amendment. In my judgment it would not be fair to the parties, and in particular AstraZeneca, to adjourn the matter at this late stage. Accordingly, I shall refuse Astex permission to re-re-amend the Particulars of Claim.

**Is AstraZeneca entitled to recover the milestone payments in respect of CD1?**

1. AstraZeneca seeks to recover from Astex the two milestone payments of $1 million which AstraZeneca paid Astex under the Agreement in respect of CD1, namely $1 million paid in **November 2010 as Program Milestone 3** (see paragraph 244 above) and $1 million paid in January 2012 as Development Milestone 1 (see paragraph 245 above), by means of a claim for restitution of money paid under a mistake. **The mistake relied upon is the mistaken belief that CD1 was a Collaboration Compound**.
2. I have already concluded that, in the light of the construction I have placed upon the Agreement and my findings of fact as to the development of CD1, CD1 was not a Collaboration Compound. This is a necessary, but not a sufficient, basis for AstraZeneca to succeed on its counterclaim.

*The law*

1. The applicable principles were briefly summarised in *Jazztel plc v Her Majesty's Revenue and Customs* [[2017] EWHC 677 (Ch)](http://www.bailii.org/ew/cases/EWHC/Ch/2017/677.html%22%20%5Co%20%22Link%20to%20BAILII%20version) at [28]-[30], where Marcus Smith J explained that the modern position is that any causative mistake of fact or law can qualify as a relevant mistake. In order to establish a *prima facie* claim to restitution of an enrichment, a party needs to show that:

i) at the time the enrichment was conferred, the claimant was mistaken; and

ii) the mistake caused the enrichment to be conferred (in the sense that, but for the mistake, the enrichment would not have been conferred).

1. As Marcus Smith J held at [30][c], the claimant may have been mistaken even if he or she harboured doubts about the matter in question:

"Mistakes can co-exist with an element of doubt. By 'doubt' is meant the claimant's conscious appreciation that the facts or law may not be as he or she believes them to be. For example, a claimant may (wrongly) believe that he or she is legally obliged to make a payment, whilst at the same time appreciating that there is an argument that he or she is not in fact obliged to make the payment at all. Such doubts are not inconsistent with mistake, provided the doubt does not overwhelm the mistake."

… In my judgment, provided the level of subjective doubt remains below the 50% threshold, a mistake can still exist."

*The facts*

1. AstraZeneca contends that, in essence, it was Dr Angst who mistakenly concluded that CD1 was a Collaboration Compound, and forced this view through the LGT, after which it remained unquestioned and became accepted wisdom in the minds of the Project Leader (Dr Fälting) and Business Development (in the person of Dr Farmery).
2. When the BACE project moved to Södertälje, Dr Angst remained in Wilmington, in a new role of Vice President Portfolio Enhancement, in which he was head of Lead Generation and Externalisation. He was now part of AstraZeneca's global governance structure, setting the Lead Generation strategy for CNS and Pain. Reports were made to Dr Angst in the LGT as part of his global governance role. The BACE project team reported, as a matter of line management, first to the Head of Chemistry at Södertälje (Jan-Erik Nyström until 2008-9, then Dr Haeberlein), who in turn reported to the local Vice-President of CNS Discovery in Södertälje, Dr Christer Nordstedt (until he left in 2007).
3. On 8 November 2005 Dr Angst gave a presentation in which he set out a new model for the governance of Lead Generation. Before MS3, the global governance level was not involved in making transition decisions. At MS3 and beyond, the local management team would make a recommendation to the global level, namely the RAMT, which would make the decision about the transition.
4. At MS3, the LGT engaged in a detailed scientific review. The proposal document had a standard format, and section 6 in the MS3 documents accurately recorded the origin of the series under consideration:

i) DHIZ MS3: "This series was developed historically via fragment based lead generation and was the result of some excellent medicinal chemistry and collaboration between Mölndal SCL, the Wilmington BACE team and Astex Therapeutics Limited."

ii) ISIN/THIP MS3: "The ISIN series was invented and established in Wilmington and subsequently developed in Södertälje."

iii) AiZ MS3: "The AiZ series was invented and established in Södertälje during 2008."

1. Following a successful presentation to the LGT, the LGT would then present the MS3 transition to the RAMT, usually at the next RAMT meeting. Dr Angst made such presentations to the RAMT – of which he was a member – for both the DHIZ and the ISIN/THIP MS3 transitions.
2. On 5 March 2007 Dr Vestlng sent Dr Nordstedt (with copies to Mr Berg, Dr Nyström and another) a summary of what he considered to be the important parts of the Agreement and pointed out that an immediate issue was the prospect of CD nomination which might mean that AstraZeneca had to pay Astex $1 million that year (in the event, this did not happen until 2010: see paragraph 244 above). Dr Vestlng's summary also referred to the requirement to pay a further $1 million upon IND approval, which was anticipated for 2008. Although the summary referred to Section 1.7, it did not refer to the definitions of AO. HO or LO, nor did it refer to the duration of the Program.
3. On 13 March 2007 Dr Vestlng sent Dr Norstedt, Mr Berg, Dr Nyström and two others an email reiterating that Program Milestone 3 was due when AstraZeneca nominated a CD, even if it was an "investigational CD", and that Development Milestone 1 was due when AstraZeneca obtained IND approval. He noted that Dr Nordstedt was not convinced that an investigational CD counted. Dr Vestlng proposed a meeting to discuss this.
4. Dr Angst recalled having a disagreement in about 2007 with Dr Nordstedt in respect of whether Södertälje's work on the BACE project was within the Agreement, which may have been as a result of the discussions considered in the preceding paragraphs. At that time, Dr Angst was the person on the LGT and the RAMT with the most detailed knowledge of the Astex collaboration. Dr Angst's view was the BACE project was covered by the Agreement. His view prevailed, and Dr Nordstedt never brought the matter up at the RAMT.
5. At the CD1 nomination meeting of the RAMT in August 2010, or shortly before, Dr Angst recalled that a question was raised by a Södertälje scientist about whether CD1 was a Collaboration Compound. Dr Christer Köhler, who headed both the RAMT and the iMed Leadership Team, asked Dr Angst for his view. Dr Angst's view was that CD1 was evolutionarily linked to Collaboration Compounds and therefore was itself a Collaboration Compound. Accordingly, he recommended payment of the $1m for Program Milestone 3. It appears that Dr Angst thought the only way for a compound to escape from being subject to royalties was to do a clean room exercise, which is why he seems to have recommended that Södertälje should perform screening using a different team.
6. The RAMT followed Dr Angst's recommendation that the milestone should be paid. Dr Angst's view was that Dr Köhler had good reason to trust Dr Angst's interpretation and judgment, because Dr Angst was the only person who knew about the Agreement. Moreover, Dr Angst was the only chemist on the RAMT at the time of CD1 nomination.
7. Dr Angst's evidence was that he did not have the authority to authorise payments to third parties. But he was clear that the Legal department was not able to make its own assessment of the science, and he did not know whether Business Development and Legal attempted to consider the issue of CD1's contractual status independently or whether they just adopted and implemented the RAMT's recommendation to pay the milestone payment. There is no evidence of any independent consideration of the matter by the Business Development or Legal departments, and therefore it is more likely than not that they just adopted and implemented the RAMT's recommendation.
8. In summary, so far as the $1m payment for Program Milestone 3 is concerned, although doubts were raised by Dr Nordstedt and the unidentified Södertälje scientist as to whether CD1 was a Collaboration Compound, Dr Angst was firmly of the view that it was and his view prevailed. As to the $1m payment for Development Milestone 1, there is no evidence that any doubts were raised in respect of that. Dr Angst's view still prevailed, and therefore the payment was made.
9. Astex contends that AstraZeneca's case based on Dr Angst being mistaken fails for three reasons: first, because Dr Angst did not have authority to authorise payments to be made; secondly, because it was not put to Dr Angst that he was mistaken; and thirdly, because no evidence was adduced by AstraZeneca from Mr Renblad, who actually authorised the payments.
10. So far as the first point is concerned, in my judgment this is immaterial. It is clear from Dr Angst's evidence that he was the key decision maker who decided that CD1 was a Collaboration Compound and therefore recommended payment of the two milestone payments.
11. Turning to the second point, I do not consider that counsel for AstraZeneca needed to put it to Dr Angst that he was mistaken. Dr Angst was clear that he was then, and remained now, of the view that CD1 was a Collaboration Compound. If, as I have concluded, CD1 was not a Collaboration Compound, then it necessarily follows that Dr Angst was mistaken.
12. As for the third point, Dr Srinivasan's evidence in relation to CD2 was that the Operations and Finance section merely followed instructions in terms of writing cheques. There is no reason to think that the position was any different in relation to CD1. Accordingly, in my judgment the absence of evidence from Mr Renblad is again immaterial.
13. Astex also pointed to the absence of evidence from Dr Fälting and Dr Farmery. As I have said, however, it is clear from Dr Angst's evidence that he was the key decision maker. Furthermore, there is no indication in the documentary evidence, nor did Dr Angst suggest, that either Dr Fälting or Dr Farmery raised any doubts as to whether CD1 was a Collaboration Compound. Accordingly, the absence of evidence from Dr Fälting and Dr Farmery is also immaterial.

*Conclusion*

1. I conclude that, at the time the payments in question were made, AstraZeneca was mistaken as to the contractual status of CD1 and that this mistake caused the payments to be made. Accordingly, AstraZeneca is entitled to restitution of the two sums of $1 million.

Expiry of the Agreement

1. I have already concluded that, as a matter of interpretation, the Agreement is capable of expiring. AstraZeneca accepted in its closing submissions that it had not been established that the Agreement had already expired, because it had not been established that AstraZeneca had ceased "pursuing pre-clinical research referable to the Results". In those circumstances, AstraZeneca sought a declaration that the Agreement will expire if AstraZeneca ceases to pursue pre-clinical research referable to the Results (on AstraZeneca's case and my conclusions, AstraZeneca is not pursuing clinical development of any Collaboration Compound or commercialising any Licensed Product). Astex contends that a declaration in that form is too vague and would not serve a useful purpose. I disagree. In my judgment the declaration would clarify that the Agreement is capable of expiring and specify the circumstances in which it will do so.

Summary of conclusions

1. For the reasons given above, I conclude that:

i) CD1 is not a Collaboration Compound;

ii) CD2 is not a Collaboration Compound;

iii) AstraZeneca is entitled to recover the two sums of $1 million which it paid Astex as Program Milestone 3 and Development Milestone 1; and

iv) the Agreement will expire if AstraZeneca ceases to pursue pre-clinical research referable to the Results.