Neutral Citation Number: [2013] EWHC 516 (Pat)

Case No: HC11C04491, HC12C02558

IN THE HIGH COURT OF JUSTICE
CHANCERY DIVISION
PATENTS COURT

Rolls Building
Fetter Lane, London, EC4A 1NL

Date: 15 March 2013

Before :

THE HON MR JUSTICE ARNOLD

- -

Between :

HOSPIRA UK LIMITED	**Claimants**
GENERICS (U.K.) LIMITED trading as MYLAN	
- and -	
NOVARTIS AG	**Defendant**

- -
- -

Simon Thorley QC and **Thomas Mitcheson** (instructed by **Taylor Wessing LLP**) for **Hospira**
Michael Tappin QC (instructed by **Bird & Bird LLP**) for **Mylan**
Andrew Waugh QC and **Miles Copeland** (instructed by **Bristows**) for **Novartis**

Hearing dates: 20-22, 25-26 February 2013

- -

Approved Judgment

I direct that pursuant to CPR PD 39A para 6.1 no official shorthand note shall be taken of this Judgment and that copies of this version as handed down may be treated as authentic.

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THE HON MR JUSTICE ARNOLD

MR JUSTICE ARNOLD :

Contents

Introduction

1. In these proceedings the Claimants ("Hospira" and "Mylan") seek revocation of European Patents (UK) Nos. 1 296 689 ("689") and 1 591 122 ("122") (collectively "the Patents"). The Patents, both of which are entitled "Method of administering bisphosphonates", concern the administration of zoledronic acid or a salt thereof (which I shall refer to as zoledronate, since that is how it is more commonly known) intravenously at intervals of at least six months for the treatment of osteoporosis. 121 is a divisional of 689, the application for which was filed on 18 June 2001. Both Patents claim priority from two priority documents filed on 20 June 2000 and 9 February 2001. The claims of 689 have recently been amended as a result of a request for limitation under Article 105a of the European Patent Convention 2000 made by the Defendant ("Novartis") to the European Patent Office. Accordingly, I shall refer to the claims as amended.

2. The Claimants attack the validity of the Patents on three grounds. The first ground is that the claims are not entitled to priority from either priority document. It is common ground that it is only necessary to consider priority from the second priority document ("PD2"). It is also common ground that, if the claims are not entitled to priority, the Patents are invalid in the light of the intervening publication Reid *et al*, "A single annual injection of the bisphosphonate, zoledronic acid, stably reduces bone turnover and increases bone density in postmenopausal osteoporosis", *Bone* 28(5), S89 (2001) ("Reid"). The second ground is that the claimed inventions are obvious over Boutsen *et al*, "Primary Prevention of Glucocorticoid-induced Osteoporosis with Intravenous Pamidronate Given on 2 Different Regimens: a Prospective Controlled Study", *Bone* 23(5), S313 (1998) ("Boutsen"). For the purposes of the obviousness attack, both parties have assumed that the Patents are entitled to priority from the first priority document. The third ground is that some of the claims are invalid for insufficiency. Counsel for Hospira dealt with obviousness while counsel for Mylan dealt with priority and insufficiency, but hereafter I shall not distinguish between them.

The witnesses

3. The Claimants' expert witness was Professor Juliet Compston. She is Emeritus Professor of Bone Medicine at the University of Cambridge School of Clinical Medicine. After obtaining a BSc in Physiology in 1967 and an MB BS in 1970, she trained as a junior doctor in various positions. Between 1973 and 1983 she was successively Medical Registrar, Research Registrar and Senior Research Registrar at St Thomas' Hospital. She received her MD in 1979. From 1984 to 1989 she was Senior Lecturer in Pathology and Honorary Consultant at University of Wales College of Medicine and University Hospital of Wales in Cardiff. Between 1989 and 2012 she was successively Senior Research Associate, Lecturer in Medicine, Reader in Metabolic Bone Disease and Professor of Bone Medicine at Cambridge and also Honorary Consultant Physician at Cambridge University Hospitals NHS Foundation Trust.

4. Prof Compston has published over 300 papers on the pathophysiology and treatment of osteoporosis and other bone diseases. Among other experiences with clinical trials, between 2003 and 2008 she served on the data safety monitoring committee for the HORIZON study (Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly), Novartis's Phase 3 study comparing yearly zoledronate infusions with placebo in post-menopausal women with osteoporosis. She is currently the Chair of the European Union Osteoporosis Consultation Panel and a trustee of the National Osteoporosis Society. She is also currently Editor in Chief of the *Journal of Bone and Mineral Research*. She has held a number of other posts in the field and has received several awards for her work.

5. Novartis' expert witness was Professor Graham Russell. He is Professor of Musculoskeletal Pharmacology in the Botnar Research Centre at Oxford University and holds a similar appointment in the Mellanby Centre for Bone Research at the University of Sheffield. He obtained a degree in Biochemistry from the University of Cambridge in 1962 and a PhD from the University of Leeds in 1965. He then joined the research group led by Dr Herbert Fleisch, who is regarded as the "father of bisphosphonates", at the Medical Research Institute in Davos, Switzerland for two years. He also spent a further year with the by then Professor Fleisch at Bern University in 1970-71. He obtained his MB ChB from Cambridge in 1970 and received his MD in 1975. From 1972 to 1976 he held posts at St Peter's College, Oxford University, the Nuffield Orthopaedic Centre and Harvard Medical School. From 1976 he was Senior Lecturer and from 1977 to 1997 Professor and Head of the Department of Human Metabolism and Clinical Biochemistry at Sheffield. From 1997 to 2000 he was Director of the Division of Biochemical and Musculoskeletal Sciences at Sheffield. From 2000 to 2006 he was Professor of Musculoskeletal Sciences at Oxford. He took up his current posts in 2006 and 2009 respectively.

6. Prof Russell has worked on topics related to calcium metabolism and bone diseases throughout his career and is author of more than 500 publications in the field. He helped to establish the National Osteoporosis Society, is a past President of the International Bone and Mineral Society and is current President of the National Association for Paget's Disease. In 2008 he was elected a Fellow of the Royal Society. He has received numerous awards.

7. Both experts are extremely distinguished scientists in the field of bone disorders, and in my view both did their best to assist the Court. Counsel for the Claimants submitted that many aspects of Prof Russell's reports were significantly qualified during cross-examination and that this called into question the objectivity with which the reports had been prepared. I do not accept this. Although Prof Russell did make some concessions during the course of cross-examination, I consider that these were on questions of degree and emphasis. He did not resile to any significant extent from the main thrust of his written evidence.

Technical background

Bones

8. The human skeleton is made up of over 200 bones and comprises approximately 15% of an individual's weight. It provides support for muscles and locomotion, serves to protect internal organs, houses bone marrow (which produces red blood cells) and acts as a store for minerals.

9. Bone is a living tissue and is metabolically active throughout life. Macroscopically, bone consists of an outer part, called cortical (or compact) bone, and an inner part, called trabecular (or cancellous) bone. Cortical bone typically forms the cylindrical structure that is seen in the shafts of long bones, such as the femur. Such bones grow in diameter by the deposition of new bone on the outside (termed periosteal apposition) and removal of bone from the inside (termed endosteal resorption). Trabecular bone, such as found within vertebral bodies, consists of a honeycomb-like structure of interconnecting rods and plates, which confers strength and resilience.

10. The relative proportions of cortical and trabecular bone vary in different parts of the body. Although both cortical and trabecular bone contain similar cells and matrix elements, cortical bone is denser. Trabecular bone has about 10 times the surface area per unit weight of cortical bone.

11. Bone tissue is made up of a mineral component and a non-mineral matrix. The mineral is mainly calcium phosphate in the form of crystals. The mineral also contains many other constituents such as carbonate, sulphate, citrate, magnesium, sodium, potassium and fluoride. Approximately 90% of the matrix is comprised of collagen fibres. The hydroxyapatite crystals bring strength and rigidity, whilst the collagen fibres ensure the flexibility of bone. Bone matrix contains many other proteins in small proportions, one of which is osteocalcin. Bones also contain blood vessels, both large and small.

Bone remodelling

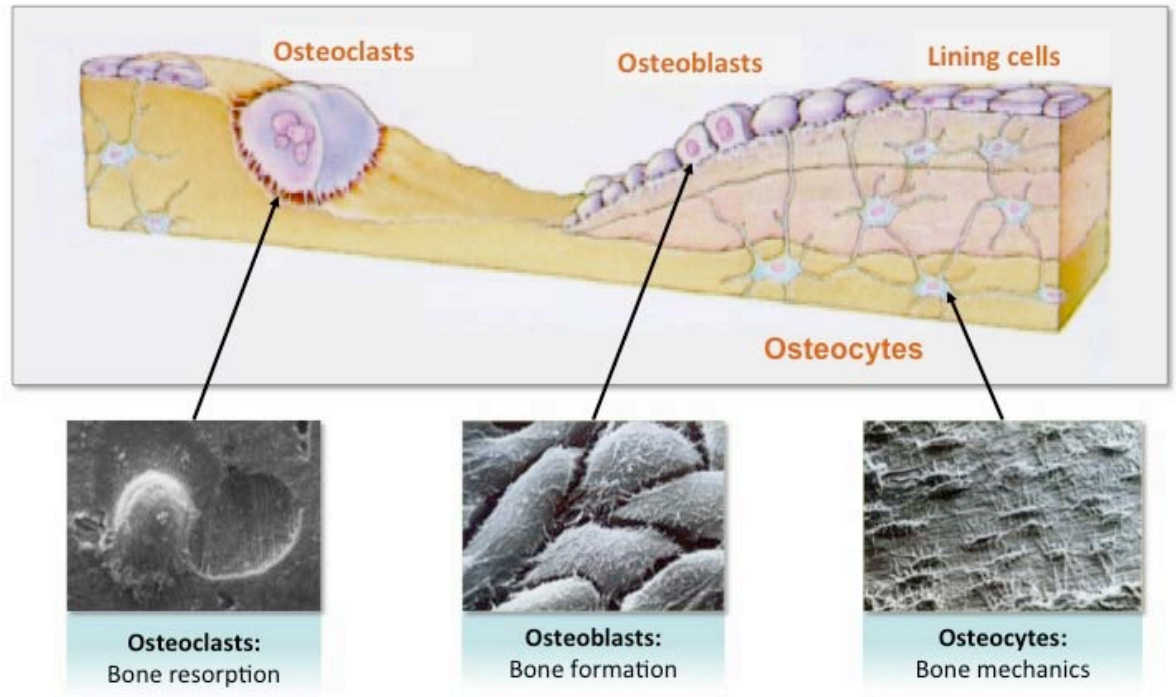
12. "Bone modelling" is the process by which the skeleton grows and changes shape. Modelling takes place principally in childhood and leads to the increase in size of bones. This process significantly reduces once the skeleton has reached its ultimate size at the end of puberty.

13. "Bone remodelling" is the process by which, throughout adult life, old bone is broken down ("resorption") and replaced by new bone ("formation") in continuous episodic cycles by the coordinated actions of specialised cells. Remodelling takes place in two

ways: (i) random (or stochastic) remodelling throughout the body maintains the skeleton, and (ii) targeted remodelling repairs the skeleton in response to damage, for example at the site of a micro-fracture or mechanical strain.

14. The rate of bone turnover changes throughout life, in response to hormonal and mechanical influences. It is believed that, in the average human, approximately 2-10% of the skeleton is renewed annually. Trabecular bone is remodelled at a much more rapid rate than cortical bone.

15. Remodelling occurs by the operation of groups of cells comprising principally of osteoclasts, osteoblasts and osteocytes. These groups of cells are termed bone remodelling units or BMUs. Each BMU consists of relatively few osteoclasts, but more osteoblasts. A diagram of a typical BMU is reproduced below. There are normally 2-5 million BMUs operating in the human skeleton at any one time, although in osteoporotic patients this number will be larger.



16. Remodelling starts by existing bone being resorbed by osteoclasts, creating resorption pits in the bone surface. The resorption pits are then refilled by osteoblasts, which deposit organic matrix into the resorption pits which, in time, calcifies.

17. Osteoclasts are multi-nucleated, giant, highly destructive cells. In the process of resorption they move across the bone surface dissolving and breaking down old bone by the secretion of hydrogen ions and enzymes into an enclosed compartment ("the ruffled border") formed between the bone surface and the part of the osteoclast in contact with the bone. Osteoclasts have a typical lifespan of approximately 2-3 weeks.

18. Osteoblasts are smaller and far less motile than osteoclasts. Osteoblasts are found clustered in groups along the bone surface. They secrete constituents of the bone matrix (including proteins and in particular collagen) on to the surface of the resorption pits, which subsequently calcify to form new bone.

19. At a given moment, some osteoblasts stop synthesising new bone material and some become embedded within bone. At this point they are called osteocytes. Osteocytes are more numerous than osteoclasts or osteoblasts. These cells remain connected to each other forming a large network, which can be likened to a network of nerve cells. Osteocytes are thought to influence the composition of bone fluid and play a role in the adaptation of bone in response to mechanical influences. In 2000, their precise role in the remodelling process was poorly understood.

20. In 2000 the bone remodelling cycle was generally believed to be substantially completed within 3-4 months. The osteoclasts work relatively quickly and bone resorption is completed within about 2-3 weeks (corresponding to the lifespan of an osteoclast). There then follows a short waiting period whilst the BMU prepares for the bone formation process. The osteoblasts work more slowly, taking 2-3 months to form and mineralise new bone.

Age and bone mass

21. For most individuals, bone mass does not rise significantly beyond the age of 25 to 30 years. After this time, for approximately the next two decades, bone mass remains at a steady level, after which time it starts to decline. This decline is generally quicker and steeper for women than men.

Metabolic bone disorders

22. Subject to the natural increase and decline in bone mass with age, in healthy individuals, equilibrium is maintained between bone resorption and formation, with osteoclasts resorbing bone and osteoblasts forming new bone. Sometimes this bone turnover mechanism can be disrupted, however.

23. All metabolic bone disorders involve disruption to the regular cyclical activity of bone resorption and formation. Such disorders can be divided into conditions of localised pathology on the one hand and systemic conditions on the other. Paget's disease is an example of a localised disease (i.e. one which only affects limited parts of the skeleton). This is in contrast to systemic conditions such as osteoporosis and osteomalacia that affect the whole skeleton. In 2000 it was generally recognised that these disorders were distinct conditions, with different profiles, causes and symptoms. They were diagnosed differently and were managed differently.

24. Cancer itself is not conventionally regarded as a metabolic bone disorder, but the skeletal complications of cancer such as hypercalcaemia have similarities to metabolic bone disorders.

25. *Osteoporosi*s. Osteoporosis is a disease characterised by low bone mass, micro-architectural deterioration of bone tissue, leading to enhanced bone fragility, and a consequent increase in fracture risk. In osteoporosis, bone remodelling is disturbed with the result that bone resorption occurs to a greater extent than bone formation. The resorption does not necessarily happen faster, but at a larger number of sites, so that overall there is more osteoclastic activity. It was generally understood in 2000 that, if fewer and/or shallower resorption pits were created by osteoclasts, it would be easier for associated osteoblasts to undertake their function and thus restore the integrity of the bone. There are various types of osteoporosis, of which by far the

most common is post-menopausal osteoporosis. Other types of osteoporosis include male osteoporosis and steroid-induced osteoporosis.

26. The most significant consequence of osteoporosis for patients is a fracture. Hip fractures are arguably the most serious outcome of osteoporosis, and are associated with considerable morbidity. It is estimated that the cost to the NHS of hip fractures alone was £1.73 billion in 2001, compared to £1.75 billion for coronary heart disease in 2004.

27. *Paget's disease*. Paget's disease is a localised chronic disorder which can result in affected bones being enlarged and misshapen. It is caused by abnormal giant osteoclasts ("Pagetic osteoclasts") which resorb bone more rapidly than normal osteoclasts (several-fold higher resorption than in osteoporosis), followed by a disorganised attempt by osteoblasts to replace resorbed bone. This results in the formation of "woven" bone (as opposed to normal lamellar bone) which is often abnormal in shape and structure and weaker.

28. The general perception in 2000 was that to treat Paget's disease the abnormal osteoclasts at Pagetic sites needed to be eliminated, and once eliminated it could take a long time for them to re-appear, if they re-appeared at all. Paget's disease accordingly was thought to require a finite course of treatment, which could be repeated as required. It was recognised that a successful course of treatment could be followed by a period of prolonged remission.

29. *Hypercalcaemia*. Hypercalcaemia merely means an elevated blood calcium level. It can be caused by excessive skeletal calcium release, i.e. excessive bone resorption from diseases such as hyperparathyroidism (due primarily to tumours of the parathyroid glands), or multiple myeloma, increased intestinal calcium absorption, or decreased renal calcium excretion.

30. *Osteomalacia*. Osteomalacia is a disease which results in poor mineralisation of bone (i.e. lack of calcification) and can result in soft bones. This can be due to inherited disorders, or more often due to lack of vitamin D. In children it is known as rickets.

Bone mineral density

31. Bone mass is assessed by measuring the bone mineral density or BMD of a patient's bone. In 2000 BMD was measured using a densitometer, which relies on the relative absorption by bone of X-rays of different energies (Dual Energy X-ray Absorptiometry or DEXA). Osteoporosis was diagnosed by reference to BMD: osteoporosis was considered to be present when a patient's BMD measurement was more than 2.5 standard deviations below the young adult reference mean.

32. In early research into the efficacy of bisphosphonates in the treatment of osteoporosis, BMD was the main measurement available to practitioners. For regulatory purposes, bone mineral density was still the recommended primary endpoint in Phase 2 clinical trials in 2000. This was because it was considered to be the best surrogate for fracture risk. (In a Phase 3 trial, the primary endpoint would be the fracture rate itself.)

Biochemical markers

33. By 2000 it was possible to detect and quantify a number of biochemical markers of bone resorption and formation.

34. Bone resorption markers included the following:

    i) Urinary hydroxyproline. Hydroxyproline is found mainly in collagen. It is not tissue-specific, and therefore by 2000 other bone resorption markers were seen as more informative and reliable.

    ii) Urinary (collagen type I cross-linked) N-telopeptide (NTX). NTX fluctuates in a sensitive manner in line with bone resorption patterns. It is often measured together with creatinine levels and expressed as a ratio of NTX/creatinine.

    iii) Urinary or serum C-telopeptide (CTX). C-terminal telopeptide (also known as carboxy-terminal collagen crosslinks) was regarded in 2000 as a very reliable biomarker for measuring the rate of bone resorption. The CTX test measures the concentration of a crosslink peptide sequence of type I collagen found in bone (and other tissues). This specific peptide sequence relates to bone turnover because it is the portion that is cleaved by osteoclasts during bone resorption, and its serum levels are therefore proportional to osteoclastic activity at the time the blood sample is drawn. The test used to detect CTX in serum is called the Serum CrossLaps test.

35. Bone formation markers included:

    i) Bone specific alkaline phosphatase (BSAP)/Serum alkaline phosphatase (SAP). Alkaline phosphatase is an enzyme produced by osteoblasts, although its precise role in bone mineralisation was not fully understood. Alkaline phosphatase is also produced by the liver and the placenta. SAP has been used for many decades to diagnose Paget's disease. SAP cannot be used to differentiate between alkaline phosphatase produced by osteoblasts and by the liver, but the high level of osteoblastic activity in Paget's disease patients means that the alkaline phosphatase produced by the osteoblasts far outweighs that produced by the liver. For osteoporosis patients, where there is much less osteoblastic activity, and SAP may not be elevated out of the normal range, BSAP is a much more useful marker.

    ii) Serum osteocalcin (OC). This protein is secreted by osteoblasts and was widely accepted as a marker for osteoblastic activity and hence bone formation although its precise function remained unknown. However, OC is released into the circulation during resorption so the serum level at any one time has a component of both bone formation and resorption.

36. In addition to the markers listed above, the hormonal marker parathyroid hormone (PTH) could be measured. PTH is a systemic hormone which indirectly stimulates differentiation of precursor cells to increase osteoclast production. It also indirectly activates osteoclasts to resorb bone.

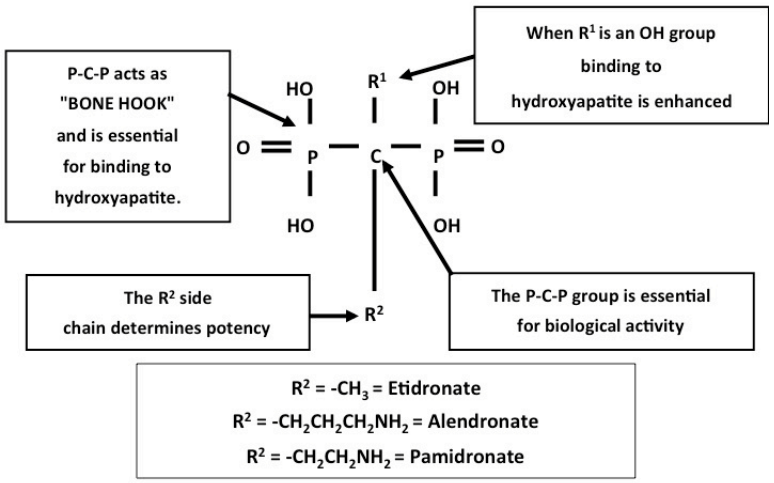
Treatments for osteoporosis

37. In 2000 there were various treatments available for osteoporosis such as hormone replacement therapy, calcium and vitamin D supplements, calcitonin and bisphosphonates. Some of these treatments were also used for other metabolic bone disorders.

Bisphosphonates

38. Bisphosphonates were originally developed as chemically stable analogues of pyrophosphates and were proposed for uses that exploited their ability to inhibit calcification (such as to inhibit vascular calcification). It was then discovered that bisphosphonates could inhibit the dissolution of bone mineral and this led to the idea that bisphosphonates could be used to slow down the rate of bone resorption.

39. The chemical structure of bisphosphonates is shown below:



40. It was known in 2000 that, as bisphosphonates have a high affinity for calcium ions, they were attracted to and accumulated on bone following administration, binding preferentially to exposed calcium-containing bone minerals on the surface in sites of bone remodelling where there was current or recent osteoclastic and osteoblastic activity. In particular, it was thought that the positioning of the two phosphonate groups with one carbon atom between them enabled the bisphosphonate to bind to bone, and that the R1 group, which is a hydroxy group in most bisphosphonates used in humans, provided an additional mineral binding ability. This is because the hydroxy group and two phosphonate groups together form a tri-dentate ligand (together these groups were known as the "bone-hook"). It was not generally thought that the R2 group had any involvement in a bisphosphonate's ability to bind to bone. Rather, the R2 group was thought to be mainly responsible for biological activity such as suppression of resorption.

41. The first clinical uses of bisphosphonates were as inhibitors of calcification, for example to prevent calcification or formation of bone in soft tissue such as kidneys or arteries, or in abnormal locations (to prevent ectopic calcification or heterotopic

ossification). Another early use of bisphosphonates was as agents for "bone scanning". By the early 1980s, the use of bisphosphonates to inhibit bone resorption in Paget's disease patients was well established – for example etidronate was first approved for Paget's disease in 1982 in Europe. At about the same time, the use of bisphosphonates in cancer patients was starting to be recognised, although it was not until the 1990s that the first bisphosphonates were approved for the treatment of skeletal events associated with cancers. It was not until the 1990s that the use of bisphosphonates in the treatment of osteoporosis became established as an important area of development (the first bisphosphonate was approved for osteoporosis in Europe in 1991).

42. The early bisphosphonates which were approved for use in the treatment of bone disorders, such as etidronate and clodronate, did not contain nitrogen in their R2 groups. Subsequently aminobisphosphonates containing nitrogen in R2, such as pamidronate, alendronate and ibandronate, were developed. These were found to be more potent (meaning that less drug was required to produce the same effect). Further research led to the development of bisphosphonates which included cyclic nitrogen-containing groups such as imidazoles, and it transpired that some of these bisphosphonates were even more potent. These included risedronate, minodronate and zoledronate.

43. The following table shows the bisphosphonates that had been approved for use or were in clinical development by 1999 (* indicates those that had been approved for one or more indications in one or more countries):

Bisphosphonate	**R1**	**R2**	**Main uses**
Etidronate*	OH	CH_3	Osteoporosis, Paget's disease
Clodronate*	Cl	Cl	Metastases, myeloma
Pamidronate*	OH	$CH_2CH_2NH_2$	Hypercalcaemia, myeloma, Paget's disease
Alendronate*	OH	$(CH_2)_3NH_2$	Osteoporosis and other indications
Risedronate*	OH	CH_2-3-pyridine	Registration pending for osteoporosis
Tiludronate*	H	CH_2-S-phenyl-Cl	Paget's disease
Ibandronate*	OH	$CH_2CH_2N(CH_3)$(pentyl)	In development, osteoporosis and other diseases
Zoledronate	OH	CH_2-imidazole	In development, several diseases

Minodronate	OH	CH_2-2-imidazo-pyridinyl	
Incadronate	H	N-(cyclo-heptyl)	
Olpadronate	OH	$CH_2CH_2N(CH_3)_2$	
Neridronate	OH	$(CH_2)_5NH_2$	
EB-1053	OH	CH_2-1-pyrrolidinyl	

44. As this suggests, as at June 2000 there were only two bisphosphonates which had been approved for the treatment of osteoporosis: etidronate (marketed by Procter & Gamble under the trade mark Didronel) and alendronate (marketed by Merck under the trade mark Fosamax).

45. In the case of etidronate, patients were directed to take one 400mg dose orally for 14 days followed by one 1.25g dose of calcium carbonate orally daily for 76 days as part of a 90 day cycle. The design of this cyclical regimen was based upon a concept known as ADFR (Activate Depress Free Repeat), but the regimen was not a true ADFR one because it did not involve an activation step. Patients were advised to avoid food for at least two hours before and after taking the medicine, particularly avoiding calcium-containing products such as milk during this time because these foods would interfere with the absorption of the drug.

46. In the case of alendronate, patients were directed to take one 10mg dose orally every day. The major side-effect of alendronate is gastrointestinal intolerance, or even oesophageal ulceration, which can be minimised if the patient takes the drug before breakfast (because food would interfere with the absorption of the drug) with a full glass of water and remains upright for 30 minutes, preferably being physically active during this time. Such administration has a negative effect on patient compliance, which can be alleviated by the development of a weekly medicine. By June 2000 it was known that Merck was proposing to market a once weekly version of Fosamax in the near future.

47. In addition to etidronate and alendronate, pamidronate was sometimes administered off-label to treat osteoporosis patients who could not tolerate those drugs. When used to treat osteoporosis, pamidronate was usually administered intravenously on a three-monthly cycle.

48. In 2000 the mechanism by which bisphosphonates suppressed bone resorption was poorly understood. Certain theories had been proposed, but none was generally accepted.

Zoledronate

49. Zoledronate was first synthesised by chemists at Ciba-Geigy (now part of Novartis) in the mid-1980s. As at June 2000, zoledronate was regarded as a relatively new bisphosphonate; it had not yet been approved for any clinical indication. It was understood that zoledronic acid was a potent bisphosphonate, meaning that smaller amounts could be given to achieve the same anti-resorptive effect as could be achieved using less potent bisphosphonates.

Modes of administration of bisphosphonates

50. Generally speaking, all of the bisphosphonates that had been approved or were under clinical investigation in 2000 were administered to patients either orally or intravenously. Oral administration had the advantage that it was simple and preferred by many patients, but intravenous administration had the advantage that it avoided the problem with gastrointestinal intolerance to which bisphosphonates were prone. A further difference was that it was known that orally administered bisphosphonates had very low bioavailability.

51. In addition, it was known that other modes of administration were potential candidates. In particular, intramuscular administration of clodronate had been approved in some countries and it was known that transdermal patches were being investigated.

PD2

52. PD2 begins by stating:

> "This invention relates to bisphosphonates, in particular to the pharmaceutical use of bisphosphonates in the treatment of conditions of abnormally increased bone turnover, such as osteoporosis."

53. The second paragraph contains some background as to the uses of bisphosphonates, explaining that bisphosphonates are used in a variety of both benign and malignant diseases in which bone resorption is increased, and as to their effects. It states:

> "The mechanisms by which bisphosphonates inhibit bone resorption are still poorly understood and seem to vary according to the bisphosphonates studied."

54. The document next acknowledges two prior art proposals to use bisphosphonates to treat osteoporosis, both of which involved daily administration for a period followed by a rest period.

55. The document then states (at page 2):

> "Surprisingly we have now found that bisphosphonates, in particular recent potent bisphosphonates, can be used for prolonged inhibition of bone resorption in conditions of abnormally increased bone turnover by intermittent administration, wherein the periods between bisphosphonate administrations are longer than was previously considered appropriate to achieve satisfactory treatment. In particular and contrary to expectation we have found that satisfactory treatment results can be obtained even when the dosing intervals greatly exceed the natural bone remodelling cycle.
>
> Accordingly the present invention provides a method for the treatment of conditions of abnormally increased bone turnover

> in a patient in need of such treatment which comprises intermittently administering an effective amount of a bisphosphonate to the patient, wherein the period between administrations of bisphosphonate is at least about 6 months.
>
> The invention further provides use of a bisphosphonate in the preparation of a medicament for the treatment of conditions of abnormally increased bone turnover in which the bisphosphonate is administered intermittently and in which the period between administrations is at least about 6 months."

56. It goes on to say that conditions of abnormally increased bone turnover which may be treated in accordance with the invention include post-menopausal osteoporosis, other forms of osteoporosis and other conditions (first paragraph on page 3). It explains that both prophylactic and curative treatment are contemplated, and says (second paragraph on page 3):

> "In particularly preferred embodiments the invention may be used for the prophylactic treatment of osteoporosis and similar diseases. Thus for example bisphosphonate may be administered to individuals at risk of developing osteoporosis on a regular basis at dosing intervals of at least about 6 months e.g. bisphosphonate may be administered routinely to postmenopausal women at dosing intervals of once every 6 months or less frequently."

57. The document then states (pages 3-4):

> "In accordance with the present invention the bisphosphonate dosing interval is at least about 6 months, e.g. once every 180 days, or less frequently, conveniently once a year, or any interval in between, e.g. one every 7, 8, 9, 10, or 11 months. Dosing intervals of greater than once per year may be used, e.g. about once every 18 months or about once every 2 years, or even less frequently, e.g. a frequency of up to about once every 3 years or less often."

58. On pages 4 and 5 it lists suitable bisphosphonates for use in the invention. These include pamidronate, alrendronate, etidronate, ibandronate, zoledronate, risedronate, tiludronate, EB-1053, minodronate, clodronate and incadronate. These are all said at page 5 to be well known from the literature. At page 6 it says that use of zoledronate is an especially preferred embodiment of the invention.

59. At page 7 the document states that the bisphosphonates (referred to as "the Agents of the Invention") may be administered in the form of pharmaceutical compositions containing a therapeutically effective amount of active ingredient optionally with carriers. It goes on:

> "The pharmaceutical compositions may be, for example, compositions for enteral, such as oral, rectal, aerosol inhalation or nasal administration, compositions for parenteral, such as

> intravenous or subcutaneous administration, or compositions for transdermal administration (e.g. passive or iontophoretic).
>
> Preferably, the pharmaceutical compositions are adapted to oral or parenteral (especially intravenous, intra arterial or transdermal) administration. Intra-arterial and oral, first and foremost intra-arterial, administration is considered to be of particular importance. …"

60. At pages 8-9 the document states:

> "The particular mode of administration and the dosage may be selected by the attending physician taking into account the particulars of the patient, especially age, weight, life style, activity level, hormonal status (e.g. post-menopausal) and bone mineral density as appropriate.
>
> The dosage of the Agents of the Invention may depend on various factors, such as effectiveness and duration of the active ingredient, e.g. including the relative potency of the bisphosphonate used, mode of administration, …. sex, age, weight and condition of the warm-blooded animal.
>
> Normally the dosage is such that a single dose of the bisphosphonate active ingredient from 0.005-20 mg/kg, especially 0.01-10 mg/kg, is administered …
>
> The dose mentioned above is typically administered intermittently with a period of at least 6 months between doses. The period between bisphosphonate administrations may be longer, e.g. conveniently once per year, once per 18 months or once every 2 years, or even longer, or any period in between.
>
> … Single dose unit forms such as ampoules of infusion solution or sold for preparation of infusion solution doses, capsules, tablets or dragees contain e.g. from about 0.5 mg to about 500 mg of the active ingredient. It will be appreciated that the actual unit dose will depend upon the potency of the bisphosphonate and the dosing interval among other things. Thus the size of the unit dose is typically lower for more potent bisphosphonates and greater the longer of the dosing interval. For example, for more potent, recent bisphosphonates such as zoledronic acid a unit dose of from about 1 up to about 10 mg may be used. For example, also for such recent, more potent bisphosphonates a unit does of from about 1 to about 5 mg may be used for dosing once every 6 months; whereas a dose of from about 2 up to about 10 mg may be used for once a year dosing
>
> Unit doses may be administered as a single or divided dose… In accordance with the invention, the time interval between administration of the last part of the divided dose and

> administration of the first part of the next, following divided dose is at least 6 months or longer, e.g. about 1 year."

61. At page 10 the document states:

> "Parenteral formulations are especially injectable fluids that are effective in various manners, such as intravenously, intramuscularly, intraperitoneally, intranasally, intradermally, subcutaneously or preferably intra-arterially."

62. On page 11 the document describes transdermal devices for administering the active ingredient.

63. There are five Examples, preceded by the statement at page 11 that in the Examples the term "active ingredient" is to be understood as meaning any one of the bisphosphonates mentioned previously.

64. Example 1 describes the preparation of capsules containing coated pellets of pamidronate. Example 2 describes the manufacture of a transdermal system containing zoledronate as the active ingredient. Example 3 describes the preparation of a 1 mg/ml solution of zoledronate for intravenous infusion. Example 4 describes the preparation of a 3 mg/ml solution of pamidronate for intravenous infusion.

65. Example 5 describes a Phase 2 multi-centre, double-blind, placebo-controlled, dose-ranging, safety and efficacy 12 month clinical trial of intravenously administered zoledronate for the treatment of post-menopausal osteoporosis. This is the same trial that was later reported in Reid. 351 patients were allocated to six study arms. Zoledronate or placebo was administered by intravenous injection. In addition to placebo, the study arms were as follows: 0.25 mg every three months; 0.5 mg every three months; 1 mg every three months; 2 mg every six months; and 4 mg every 12 months (i.e. once). Patients were evaluated every three months over the year.

66. Efficacy was ascertained by measurement of percent change from baseline in BMD by DEXA as compared to placebo at 6, 9 and 12 months. In addition, the degree and suppression of the following biochemical markers was measured every three months: PTH, BSAP, CTX, OC, NTX/creatinine ratio, urine deoxypyridinoline/creatinine ratio and urine pyridinoline/creatinine ratio.

67. The BMD results are summarised in a table on page 16. As the document states at page 15:

> "The 12 month results showed that all treatment arms demonstrated a percent change from baseline in BMD significantly ($p<0.001$) greater than placebo and not dissimilar one from another."

68. The document does not include any biochemical marker data, but states at page 16:

> "Suppression of biochemical markers of bone formation and bone resorption confirmed and supported the BMD results, demonstrating suppression of bone turnover to the pre-

> menopausal level throughout the 6 and 12 month dosing intervals."

69. The following conclusion is drawn at page 16:

> "The BMD data indicate that zoledronic acid dose administration as infrequent as every 6 or 12 months can safely result in a statistically significant and medically relevant bone mass increase. It is believed that these data further indicate that a continued preservation of new bone beyond one year, without additional dose administration, is likely or that further bone mass increase is possible. It is also believed that re-treatment in additional cycles of every 6-month, 12-month, or less frequent dose administration will lead to further BMD increase. A reduction of risk of osteoporotic fracture is expected to accompany the bone mass increase."

70. The abstract states as follows:

> "Bisphosphonates, in particular recent more potent bisphosphonates such as zoledronic acid and derivatives, can be used with satisfactory results for the prolonged inhibition of bone resorbtion in conditions of abnormally increased bone turnover, eg osteoporosis, by intermittent administration, wherein the periods between bisphosphonate administrations are longer than was previously considered appropriate, e.g. a dosing interval of at least about 6 months or less frequently."

The Patents

71. There is no substantive difference between the specifications of the Patents. There are certain differences between the specifications of the Patents and PD2, however. I would particularly highlight the following changes to PD2.

72. First, the words "nitrogen-containing" have been inserted in place of the word "recent" in the first sentence of the first of the three paragraphs from page 2 of PD2 quoted in paragraph 55 above (Patents at [0005]).

73. Secondly, the second of those three paragraphs has been omitted.

74. Thirdly, the third of those three paragraphs has been changed to refer to zoledronate instead of "a bisphosphonate" and "the bisphosphonate" (Patents at [0008]). The same change has been made in the remainder of the document, for example in the sentence beginning "Thus for example" quoted in paragraph 56 above (Patents at [0008]), the passage quoted in paragraph 57 above (Patents at [0009]), the passage referred to in the first sentence of paragraph 59 above (Patents at [0015]-[0017]), the passage quoted in paragraph 60 above (Patents at [0023], [0025] and [0026]), and the statement referred to in paragraph 63 above (Patents at [0035]).

75. Fourthly, the lists of suitable bisphosphonates for use in the invention have been omitted.

76. Fifthly, the second of the two paragraphs quoted in paragraph 59 above has been amended to delete all references to "intra-arterial" and substitute references to "sub-cutaneous, intramuscular" and (twice) "intravenous" (Patents at [0020]).

77. Sixthly, the last two sentences of the fifth paragraph quoted in paragraph 60 above have been amended as follows (Patents at [0026]):

> "For example, for ~~more recent, potent bisphosphonates such as~~ zoledronic acid a unit dose of from about 1 up to about 10 mg may be used for parenteral, e.g. intravenous, administration. ~~For example, also for such recent, more potent bisphosphonates~~ ~~a~~ A unit dose of from about 1 to about 5 mg may be used parenterally for dosing once every 6 months; whereas a dose of from about 2 up to about 10 mg may be used for once a year parenteral dosing."

78. Seventhly, Example 1 has been omitted. (The remaining Examples have not been renumbered and Example 4 has been retained.)

The claims

79. The claims of 689 in issue are as follows:

> "1. Use of [zoledronic acid] or a pharmaceutically acceptable salt thereof or any hydrate thereof in the preparation of a medicament for the treatment of osteoporosis in which the [zoledronic acid] or a pharmaceutically acceptable salt thereof or any hydrate thereof is administered intravenously and intermittently, and in which the period between administrations is at least about 6 months.
>
> 2. Use according to claim 1, wherein the period between administrations is at least about once a year.
>
> 5. Use of [zoledronic acid] or a pharmaceutically acceptable salt thereof or any hydrate thereof for the preparation of a medicament for the treatment of osteoporosis wherein said medicament is adapted for intravenous administration in a unit dosage form which comprises from about 1 up to about 10mg of [zoledronic acid] or a pharmaceutically acceptable salt thereof or any hydrate thereof, wherein the period between administrations of bisphosphonate is at least about 6 months.
>
> 6. Use according to claim 5, wherein the unit dosage form comprises from about 1 up to about 5 mg and the period between administrations is about once every six months.
>
> 7. Use according to claim 5, wherein the unit dosage form comprises from about 2 up to about 10 mg and the period between administrations is about once a year."

80. The claims of 122 in issue are as follows:

> "1. Zoledronic acid or a pharmaceutically acceptable salt thereof or any hydrate thereof for use in a method of treating osteoporosis in which the zoledronic acid or the pharmaceutically acceptable salt therefore or the hydrate thereof is administered intravenously and intermittently and in which the period between administrations is at least about 6 months.
>
> 2. Zoledronic acid or a pharmaceutically acceptable salt thereof or any hydrate thereof for use according to claim 1 wherein the osteoporosis is postmenopausal osteoporosis.
>
> 6. Zoledronic acid or a pharmaceutically acceptable salt thereof or any hydrate thereof for use according claim 1 wherein the period between administrations is at least about a year.
>
> 7. Zoledronic acid or a pharmaceutically acceptable salt thereof or any hydrate thereof for use according to any one of the preceding claims wherein the period between administrations is one year."

The skilled team

81. A patent specification is addressed to those likely to have a practical interest in the subject matter of the invention, and such persons are those with practical knowledge and experience of the kind of work in which the invention is intended to be used. The addressee comes to a reading of the specification with the common general knowledge of persons skilled in the relevant art, and he (or she) reads it knowing that its purpose is to describe and demarcate an invention. He is unimaginative and has no inventive capacity. In some cases, such as the present one, the patent may be addressed to a team of persons having different skills.

82. There is little dispute as to the skilled team to whom the Patents are addressed. The Claimants contend that they are directed to a medical practitioner with experience in the treatment of osteoporosis assisted by a clinical pharmacologist and a statistician. Novartis contend that the Patents are addressed to a team of researchers investigating treatments for metabolic bone disorders. The distinction between these formulations is that the Claimants contend that the team would be led by the clinician, whereas Novartis contend that the team would be led by a medical researcher. In my view this makes no real difference.

Common general knowledge

83. I reviewed the law as to common general knowledge in *KCI Licensing Inc v Smith & Nephew plc* [2010] EWHC 1487 (Pat), [2010] FSR 31 at [105]-[115]. That statement of the law was approved by the Court of Appeal [2010] EWCA Civ 1260, [2011] FSR 8 at [6].

84. In the present case it is common ground that Professor Fleisch's handbook *Bisphosphonates in Bone Disease: From the Laboratory to the Patient* (4th edition) ("the Fleisch Handbook"), which was published in May 2000, is reflective of the common general knowledge as at the first priority date of 20 June 2000. Accordingly, there is little or no dispute that the matters I have set out in the technical background section of this judgment were all part of the skilled team's common general knowledge. There are a number of points with respect to which there is some dispute, however. Some of these points are not directly relevant to the other issues in the case in themselves, but feed into other points which are directly relevant.

Extrapolation between different bone disorders

85. The first topic is the extent to which the skilled team would have regarded it as possible to extrapolate between different bone disorders. In particular, if a particular dosing regimen was disclosed as being effective for Paget's disease, to what extent would the skilled team have regarded that information as applicable to osteoporosis? Prof Russell's evidence was that the skilled team would not consider that one could extrapolate in that manner, but he accepted that people did use information gained from studies of Paget's disease in relation to osteoporosis. Prof Compston emphasised that both diseases involved the same abnormality of increased bone resorption, but she accepted that, if a long-lasting effect was shown in Paget's disease, one could not extrapolate that to give an expectation of a similar effect with osteoporosis. The conclusion which I draw from the evidence as a whole is that the skilled team would have regarded information derived from studies of Paget's disease as of relevance to the treatment of osteoporosis, but they would not expect to be able simply to translate dosing regimens from one to the other.

Extrapolation between different bisphosphonates

86. The second topic is the extent to which the skilled team would have regarded it as possible to extrapolate between different bisphosphonates. If one bisphosphonate was shown to be effective in the treatment of Paget's disease would the skilled team expect it to be effective for osteoporosis? If a particular dosing regimen was disclosed as being effective with one bisphosphonate, to what extent would the skilled team have regarded that information as applicable to another bisphosphonate even for the same condition?

87. Prof Russell and Prof Compston were agreed that there was little understanding of the structure-activity relationship in bisphosphonates in 2000. Accordingly, it was not possible to predict the pharmacological properties of a bisphosphonate, and in particular its potency, from its structure alone. As the Fleisch Handbook puts it at 30:

> "Each bisphosphonate has its own physicochemical and biological characteristics. This variability in effect makes it impossible to extrapolate with certainty from data for one compound to others, so that each compound has to be considered on its own, with respect to both its use and its toxicology."

Accordingly, Prof Compston accepted that one could not extrapolate from one bisphosphonate to another for efficacy or safety without actually doing the experiment.

88. On the other hand, it was known that, as stated above, aminobisphosphonates tended to be more potent than ordinary bisphosphonates, and those with cyclic nitrogens more potent still. Moreover, Prof Russell accepted that, if a particular bisphosphonate had demonstrated potential in Paget's disease, then it was expected that it could be used to reduce bone turnover in osteoporosis. More generally, he agreed that the following statement from a review he published with two co-authors in 1999 (*Osteoporosis Int* (1999) Suppl. 2: S66-80 at 74) represented conventional wisdom: "It is likely that any of the bisphosphonates that have been used clinically could be effective in osteoporosis if administered at appropriate doses." It is clear, however, that the words "at appropriate doses" are important here, and that one should add "and by appropriate methods and intervals of administration". Thus the skilled team would know that they would have to experiment to find out appropriate doses, methods, and intervals of administration.

Failures of bisphosphonates

89. Novartis contend that the skilled team would be aware that there had been a number of failures in the development of bisphosphonates for osteoporosis, but the Claimants dispute this. Novartis rely upon four such failures, as to which the position is as follows.

90. *Tiludronate*. It was announced at the Second Joint Meeting of the American Society for Bone and Mineral Research and the International Bone and Mineral Society in San Francisco in December 1998 that two multi-centre, randomised, double-blind, placebo-controlled Phase 3 studies of intermittent cyclical administration of tiludronate to a total of 2316 post-menopausal women did not produce an increase in spinal BMD or a clinically relevant decrease in fractures. Fleish reports this as follows at 152:

> "… in a large multicentre study on osteoporotic women, either 50 or 200 mg given orally for 7 days each month, were effective neither on bone mineral density nor on the fracture rate."

91. Prof Compston accepted that it was generally known in June 2000 that tiludronate was ineffective in this dosing regimen, although she thought that this was widely attributed to use of the wrong dose, which had not been tested in a Phase 2 trial.

92. *Ibandronate*. The Fleisch Handbook refers at 151 to the fact that two large Phase 3 trials of ibandronate were then underway. Prof Compston accepted that it was announced at the International Osteoporosis Foundation World Congress on Osteoporosis in Chicago on 18 June 2000 that the trials had been unsuccessful, that this was big news at the time and that "all the major players" in the field would have heard of the failure at the Congress. It is plain, however, that no one who was not present at the Congress would have known about this just two days later. Accordingly this cannot have been common general knowledge. For what it is worth, Prof Compston again thought that the failure was due to the wrong dose.

93. *Risedronate*. It was put to Prof Compston, and she accepted, that risedronate had been shown to work in some patients, not others. This was based on a paper published in 2002, however. There is nothing to show that this was common general knowledge in June 2000. To the contrary, the Fleisch Handbook states at 151-152 that risedronate was effective in prevention of bone loss in early post-menopausal women.

94. *Incadronate*. There is no evidence at all that incadronate was known to have failed as at June 2000.

Duration of action of bisphosphonates

95. There are two closely-related issues under this heading. First, Novartis contends that it was generally thought in June 2000 that bisphosphonates had a rapid offset of action, whereas the Claimants dispute this. Secondly, Novartis contends that it was generally thought that bisphosphonates which had become "buried in the bone" were inactive, whereas the Claimants suggest that it was thought that bisphosphonates could be slowly released from the bone and thereby achieve a long duration of action.

96. So far as the first point is concerned, Prof Russell's evidence was that there was a broad scientific consensus that the effects of bisphosphonates wore off rapidly after the discontinuation of treatment. Prof Compston agreed that it was known that the effect of *orally* administered bisphosphonates, and in particular alendronate, wore off rapidly upon cessation of administration; but her view was that there was evidence for prolonged action of *intravenously* administered bisphosphonates. I accept that that was her opinion at the time, but it appears to me that the common general knowledge was as stated by the Fleisch Handbook at 148 (emphasis in the original):

> "There are not many studies examining the consequences of discontinuing bisphosphonate administration. It appears that the results depend on the bisphosphonate administered, the dose, and the length of treatment. In general, bone turnover increases again within 3 months and reaches pre-treatment levels within a year.
>
> …
>
> *After discontinuation of treatment bone turnover returns to pre-treatment values within months and bone loss appears to resume again, although later.*"

97. So far as the second point is concerned, Prof Russell's evidence was that it was generally understood that bisphosphonate buried in the bone remained inactive, at least as long as it remained buried there. It was thought that this was why bisphosphonates had a limited duration of action: they remained active while on the bone surface, but rapidly became buried or detached from the surface. This evidence is supported by a statement in the Fleisch Handbook at 143: "These results suggest that the bisphosphonate buried in bone is inactive…" Prof Russell acknowledged that, in the case of Paget's disease, some had postulated that buried bisphosphonates could be recycled, but said that this was not generally accepted, and certainly not in relation to osteoporosis.

98. Prof Compston agreed that it was generally understood that bisphosphonates remained in the bone for a long time, but her view was that, in the case of *intravenously* administered bisphosphonates, this was slowly released during remodelling leading to a long duration of action in osteoporosis as well as Paget's disease. She was candid, however, that she had no explanation as to why there should be a difference between intravenously and orally administered bisphosphonates in this respect. Again, I accept that her opinion was as she stated, but I am not persuaded that it represented the common general knowledge in June 2000. No such distinction is made in the Fleisch Handbook.

Dosage regimens exceeding three months

99. The most disputed issue is whether, as Novartis contends, it was the general perception that dosage regimens exceeding three months would be ineffective for the treatment of osteoporosis. There are a number of aspects to this dispute, two of which I have already addressed separately in the preceding section of this judgment.

100. Prof Russell's written evidence was that many workers in the field thought it was necessary to administer bisphosphonates at least once during the 2-3 week lifecycle of an osteoclast in order to treat osteoporosis effectively, and therefore that the period between the administration of doses should be no longer than 2-3 weeks; while others thought that it would be possible to achieve effective dosing in accordance with the 3-4 month lifecycle of the BMU, although in his opinion this was less logical. As he put it in paragraph 138 of his first report, "The general perception was that dosage regimens exceeding 3 months would be ineffective for the treatment of osteoporosis."

101. In cross-examination Prof Russell put less emphasis on the perceived relevance of the 2-3 week osteoclast lifecycle, and more on the perceived relevance of the bone remodelling cycle. Subject to that, however, he maintained that the general perception was as he had stated in his reports, as can be seen, for example, from the following extract:

> "Q. But if they felt that there was a ceiling of three months, they would never have said 2-4?
> A. I am not sure they would never have said, because even the best of us can be inconsistent in what we sometimes say**.** I do really think that this remodelling cycle, three month, is a really important concept because if you imagine what happens when you give a bisphosphonate, you have osteoclast [*a*]round, the bisphosphonate inactivates them. You know, for a period of time, the bisphosphonate has virtually disappeared and sooner or later osteoclasts are going to come back. By the end of a three month, all those remodelling cycles which have been busy filling in their space, you know, will have done that and there will be a whole new, what, 5 million units of remodelling coming back into play. So I really think that this is an important part of it. And we see it, you know, so often stated. I think there are more people who refer to the osteoclast lifecycle and the remodelling cycle as influencing their thinking than those who do not care about that. Let us put it that way."

102. Prof Compston disagreed that there was a general perception that dosage regimens

exceeding three months would be ineffective. She accepted that there were a number of instances of bisphosphonates being dosed on a three-month regimen, particularly intravenously, but it was her view that this was at least partly a historical legacy from the ADFR concept which had been discredited by June 2000. The main example of this was etidronate, the three-month administration cycle for which she agreed had been chosen because it roughly equated to the bone remodelling cycle. She also acknowledged that bisphosphonates were orally administered at much shorter intervals, but explained that this was because longer intervals required larger doses which would be more likely to cause gastrointestinal side effects.

103. In support of her view, Prof Compston relied in particular on two related papers, Vasikaran *et al*, "Sustained Response to Intravenous Alendronate in Postmenopausal Osteoporosis", *Bone* 17(6): 517-520 (1995) and Khan *et al*, "Elimination and Biochemical Alendronate in Postmenopausal Osteoporosis", *J. Bone Min. Res.* 12(10): 1700-1707 (1997). Of the two, Khan is the more important since it is both later and builds upon Vasikaran.

104. Vasikaran studied the effect of administering 7.5 mg of alendronate intravenously for four days to 15 patients with post-menopausal osteoporosis by means of BMD, urine hydroxyproline, SAP, OC, PTH and calcium measurements over a period of six months. The authors stated at 519:

> "The most interesting observation that we observed was that biochemical evidence for the inhibition of bone resorption persisted for at least 6 months after a 4 day exposure to alendronate. Our observations suggest that treatment with alendronate does induce effects on bone turnover in osteoporosis in much the same manner as observed in Paget's disease. This finding is in contrast to the results reported by Adami *et al* using a lower dose (5 mg) and a single infusion of alendronate in which the effect wore off within weeks of stopping treatment. This may be due to the lower dose given (5 vs 30 mg)."

105. Khan studied the effect of administering 7.5 mg of alendronate intravenously for four days to 21 patients with post-menopausal osteoporosis by means of BMD, urine hydroxyproline, SAP, OC, PTH and calcium measurements for a period of two years. In this study the authors evaluated both the pharmacokinetics and the pharmacodynamics of alendronate. The authors stated at 1705-1706 (omitting footnotes):

> "Although the lack of a control group limits the conclusions on the duration of the therapeutic response, the significant changes observed in the biochemical indices were greater than the long-term coefficient of variation for each variable. Exposure to a short course of alendronate in high doses thus appears to induce a prolonged effect on bone resorption, which remained significantly below pre-treatment values for at least 1 year and probably 2 years following treatment. The effects on BMD would support this view. … The effects of oral treatment on bone resorption are similar, suggesting that the

> pharmacodynamic response over the first year may depend on the total dose given rather than the duration of exposure."

106. This gave rise to a dispute between the parties as to whether these papers, or at least their broad thrust, formed part of the common general knowledge. Prof Compston's evidence was that the papers had attracted a lot of interest in the field and were well known. Prof Russell disagreed with this, although he personally was aware of the work since some of the authors were based in his department. Prof Russell pointed out that he had not referred to either of the papers in his 1999 review. As for the Fleisch Handbook, this listed Khan among a list of original articles on alendronate as part of a longer list of "recommended selected reading" at the end of the chapter on osteoporosis, but Khan does not appear to be reflected anywhere in the text. Khan appears only to have been cited 11 times in papers published by the end of 2000 and Vasikaran only 12 times. In these circumstances I am not satisfied that either paper, or their broad thrust, was common general knowledge as at June 2000.

107. Counsel for the Claimants also relied upon a number of other pre-priority date papers which he put to Prof Russell in cross-examination. He did not suggest that these were common general knowledge in themselves. Rather he submitted that they demonstrated that a number of workers in the field had either actually tried longer intervals between intravenous administrations of bisphosphonates than three months or at least had suggested this, and that this showed that there was no general perception that dosage regimens exceeding three months would be ineffective. I am unimpressed with this. Apart from Vasikaran/Khan and Boutsen *et al* (as to which, see below), only two groups appear to have actually tried a longer period. One was Adami *et al*, which is referred to in the passage quoted in paragraph 108 below, but the relevant paper is not in evidence. The other was Filiponni *et al*, "Intermittent Versus Continuous Clodronate Administration in post-menopausal Women with Low Bone Mass" *Bone* 26(3): 269-274 (March 2000). They tested clodronate administered every six months over two years, but even then their concluding suggestion at 274 was that "an optimal dosage could well be 1200 mg by intravenous infusion repeated every 4 months". There are also a couple of other papers containing suggestions for regimens of longer than three months, but they are somewhat tentative.

108. Counsel for the Claimants also put to Prof Russell a passage from "The Use of Bisphosphonates in Osteoporosis" by Professor Fleisch, Chapter 9 in *Osteoporosis* edited by Stevenson and Lindsay (1998) at 194-195 which I think is worth quoting in full:

> "Little is known yet about the best mode of administration of these compounds. Is there any advantage in discontinuous versus continuous administration? One study in rats showed no difference when tiludronate was given over a period of 16 weeks at the same total dose for five days every four weeks or five days a week (Ammann *et al*., 1993). If discontinuous treatment was used, what would be the best regimen? There is no proof that the regimen prescribed for etidronate is optimal. Indeed, the ADFR theory, if it is applicable at all, may well be inapplicable to a drug with a long-term action. A single administration of pamidronate every three months actively increased bone mineral density in various sites (Thiébaud *et al*.,

> 1994). Recently it was shown that 10 mg of alendronate infused over five days was effective on bone turnover for 720 days in Paget's disease, 120 days in metastatic bone disease, 124 ± 82 days in postmenopausal osteoporosis, 28 ± 32 days in primary hyperparathyroidism and only 12 ± 9 days in humoral hypercalcemia of malignancy (Adami *et al*., 1992). This might raise the possibility of a biannual treatment in osteoporosis and, since the duration probably depends on the dose, a less frequent treatment may even be envisaged. However, since the total dose is most probably the relevant one, the less frequent the administration, the higher the individual dose, which might present drawbacks, the continuous administration having the advantage of lower peak blood levels.
>
> The optimal dose will have to be determined for each bisphosphonate. It should be chosen such that bone turnover is not decreased excessively, but bone loss is still inhibited adequately, or better yet, bone is gained.
>
> Many other questions remain. For example, do differences exist between various bisphosphonates? Will it be of advantage to administer the bisphosphonates together with a compound which increases bone formation, such as fluoride? Should these compounds be used both for treatment and for prevention of disease?"

109. Prof Russell's evidence was that this passage reflected the uncertainty in the field at the time and that the position remained the same two years later.

110. To similar effect is the following concluding passage, headed "Future Prospects", in the Fleisch Handbook at 181:

> "The bisphosphonates represent an important development in the field of treatment of bone diseases, and it is probably that we are only at the beginning of a new era of therapy.
>
> Many issues are still unresolved. For example, we do not yet know whether we have found the optimal regimen for the various compounds available. This is especially the case in treatment of osteoporosis. How can the intravenous versus the oral therapy be compared? Is there an advantage to the use of an intermittent therapy? Are the newly proposed regimens of a weekly tablet, or of a 3-monthly injection, just the first step in a new evolution? Could one use longer intervals, possibly even once yearly treatment? Which are in the different cases the optimal regimens for the various bisphosphonates? Will there be an advantage in the future to combine bisphosphonates, or bisphosphonates with another inhibitor of resorption, such as estrogens in hormone replacement therapy, as is already done by some clinicians, SERMS, or with stimulator of bone formation?

> …
>
> Since the long persistence of bisphosphonates in the body is a concern for some, it may be possible in the future to devise drugs that are similar to the bisphosphonates, have similar effects, but are metabolically broken down.
>
> ….
>
> Lastly, it could be that with a still better knowledge of the mode of action of these compounds at the cellular level, new insight will be gained into the physiological and pathophysiological function of bone, opening up new approaches to therapy."

111. The conclusion I reach in the light of all the evidence is that it was generally considered that appropriate doses of suitable bisphosphonates intravenously administered at intervals of three months would be likely to be effective in the treatment of osteoporosis. As both Prof Compston and Prof Russell agreed, that was where the bulk of the evidence was. I am not convinced that there was a general perception that administration at intervals of more than three months would be ineffective, but nor am I convinced that it was thought that administration at such intervals would be likely to be effective. Rather, it seems to me that the general picture is one of considerable uncertainty as to whether administration at longer intervals would be efficacious or not. Given the paucity of available data, the skilled team would be conscious that the only way in which to find out whether administration at longer intervals was efficacious was by experiment.

The significance of biomarker data

112. Another important area of controversy concerns the significance that the skilled team would attach to biochemical marker data, and in particular to biochemical marker results as compared to BMD results.

113. Prof Russell's evidence was BMD data were recognised to respond much more slowly to any given treatment than biochemical marker measurements, owing to the fact that the change in bone mineral density depended in large part on the filling in of the remodelling spaces, which took several months. Accordingly, BMD data were only useful in monitoring efficacy after a year or more of treatment where biochemical markers gave an indication of response to therapy within 6-12 weeks of commencement. Furthermore, for comparisons of different dosage regimens, biochemical markers offered a clearer picture than changes in BMD, especially in the short term, because the percentage changes in BMD in osteoporotic patients were comparatively small and thus error margins were more significant.

114. Prof Compston agreed that biochemical markers provided a good indication of whether a treatment would be effective in suppressing bone resorption and that they responded more quickly to changes induced by drug treatment than BMD, but she said that they were not considered to be as good a surrogate for fracture risk as BMD.

115. The conclusion I draw from this evidence is that, for long term evidence of reduction

in fracture risk, the skilled team would place more weight on BMD data; but that, for shorter term evidence of efficacy in suppressing bone resorption, particularly in the context of comparing dose regimens, the skilled team would place more weight on biomarker data, particularly CTX data.

116. As to the length and degree of suppression of biochemical markers that the skilled team would be looking for, there was little, if any, disagreement between Prof Russell and Prof Compston that they would be looking for a sustained 40-50% reduction in bone resorption markers.

Zoledronate

117. There is some disagreement as to precisely how much the skilled team would have known about zoledronate from their common general knowledge. It is common ground that it was well known that zoledronate was under investigation for the treatment of Paget's disease and skeletal complications of cancer. The Claimants contend that it was also generally known to be under investigation for osteoporosis, but Novartis disputes this. Prof Compston's evidence was that she was aware of this at the time, but Prof Russell was not sure when he became aware of this. I am not satisfied that this was common general knowledge in June 2000. Still less am I satisfied that it was common general knowledge that zoledronate was administered intravenously in the studies that had been undertaken.

118. More specifically, Novartis presented the results of a Phase 3 trial of single intravenous doses of 4 mg and 8 mg of zoledrate to treat hypercalcaemia in cancer patients at a meeting of the American Society of Clinical Oncology in New Orleans on 22 May 2000. Novartis publicised this in a press release issued on the same day and the information was reported in at least one industry publication, *The Pink Sheet*, published on 29 May 2000. Counsel for the Claimants appeared to suggest in his closing submissions that this would have been common general knowledge by the priority date, but I do not accept that.

Construction

119. The general principles applicable to the construction of patent claims were summarised by Jacob LJ in *Virgin Atlantic Airways Ltd v Premium Aircraft Interiors UK Ltd* [2009] EWCA Civ 1062, [2010] RPC 8 at [5].

120. In the present case both counsel assured me that there was no issue as to the construction of the claims. In particular, it is common ground that the words "for the treatment of osteoporosis" are to be interpreted as meaning that the regime is in fact effective for the treatment of osteoporosis.

121. Nevertheless, it became apparent during the closing submissions that there was a lurking issue as to construction. This arises out of the fact that many of the claims are open-ended, in the sense that they either have no upper limit to the period between administrations of zoledronate or they have no upper or lower limit to the dose of zoledronate or both.

122. Counsel for Novartis submitted that the correct approach to the construction of such open-ended claims was that adopted by the European Patent Office. This is

conveniently summarised in *Case Law of the Boards of the Appeal of the European Patent Office* (6th ed) at 245-246 as follows (emphasis added):

> "The patent claims must clearly define the subject-matter for which protection is sought under Art. 84 EPC. In T 94/82 (OJ 1984, 75) it was held that this requirement was fulfilled in a claim to a product when the characteristics of the product were specified by parameters relating to the physical structure of the product, provided that those parameters could be clearly and reliably determined by objective procedures which were usual in the art. In such a product claim, it sufficed to state the physical properties of the product in terms of parameters, since it was not mandatory to give instructions in the claim itself as to how the product was to be obtained. The description, however, had to fulfil the requirements of Art. 83 EPC 1973 and thus enable the person skilled in the art to obtain the claimed product described in it (see also T 487/89, T 297/90, T 541/97). *Nor should this be understood as also referring to those variants falling under the literal wording of the claim but which the skilled person would immediately exclude as being clearly outside the scope of practical application of the claimed subject matter, for example, claims including an open ended range for a parameter where it was clear for a skilled person that the open-ended range was limited in practice. Values of the parameter not obtainable in practice would not be regarded by the skilled person as being covered by the claims and thus could not justify an objection of insufficiency of disclosure (T 1018/05).*"

123. In addition to T1018/05 *Sango Co Ltd/Method and apparatus for forming an end portion of a cylindrical member* at [2.3], counsel for Novartis also cited T847/89 *Asahi KKK/High tenacity polyhexamthylene adipamide fibre* at [3.5] and T624/08 *Evonik Stockhausen AB/Superabsorbent polymers having improved processability* at [3.2.2]-[3.2.3] as supporting this approach.

124. Counsel for the Claimants did not dispute that this was the correct approach to the construction of open-ended claims. Rather, he submitted that applying this approach to the construction of the open-ended claims in the present case led to the conclusion that they were properly to be interpreted as embracing all intervals of administration and all dose ranges which were in fact effective to treat osteoporosis. Furthermore, he submitted that, in the case of the interval of administration, while the skilled team would immediately appreciate that an interval of 100 years was not intended to be covered by the claims, they would interpret the claims as potentially covering intervals of 5 or 10 years, or possibly even longer. Similarly, in the case of the dose, while the skilled team would immediately appreciate that neither vanishingly small doses nor impracticably large ones were covered, they would interpret the open-ended claims as potentially extending some way beyond the specific ranges mentioned in claims 5 and 7 of 689.

125. Counsel for Novartis had no real answer to this submission and I accept it.

Priority

The law

126. In order for a claimed invention to be entitled to priority from an earlier application, it must, in the words of section 5(2)(a) of the Patents Act 1977, be "supported by matter disclosed" in that earlier application. Article 87(1) EPC expresses the requirement as being that priority can only be accorded in respect of "the same invention" as one in the earlier application. Section 5 is one of the sections which is declared to be intended to have the same effect as the corresponding provision of the EPC: see section 130(7).

127. In case G2/98 [2001] OJEPO 413, [2002] EPOR 167 the Enlarged Board of Appeal of the European Patent Office equated "the same invention" in Article 87(1) with "the same subject-matter" in Article 87(4). It expressed the requirement for claiming priority as follows:

> "The requirement for claiming priority of 'the same invention', referred to in Article 87(1) EPC, means that priority of a previous application in respect of a claim in a European patent application in accordance with Article 88 EPC is to be acknowledged only if the skilled person can derive the subject-matter of the claim directly and unambiguously, using common general knowledge, from the previous application as a whole."

128. The Court of Appeal explained this requirement in *Unilin Beheer NV v Berry Floor NV* [2004] EWCA Civ 1021, [2005] FSR 6 at [48] as follows:

> "The approach is not formulaic: priority is a question about technical disclosure, explicit or implicit. Is there enough in the priority document to give the skilled man essentially the same information as forms the subject-matter of the claim and enables him to work the invention in accordance with that claim?"

129. As Kitchin J (as he then was) observed in *Abbott Laboratories Ltd v Evysio Medical Devices plc* [2008] EWHC 800 (Pat), [2008] RPC 23 at [228], after citing G2/98 and *Unilin v Berry*:

> "So the important thing is not the consistory clause or the claims of the priority document but whether the disclosure as a whole is enabling and effectively gives the skilled person what is in the claim whose priority is in question. I would add that it must 'give' it directly and unambiguously. It is not sufficient that it may be an obvious development of what is disclosed."

130. An issue which arises in the present case is the status of the abstract in PD2. Counsel for Novartis relied on this as being part of the disclosure of PD2 for the purposes of priority. Counsel for the Claimants submitted that the abstract could not be relied on for that purpose. In support of that submission he relied upon what I had said in *Abbott Laboratories Ltd v Medinol Ltd* [2010] EWHC 2865 at [65]-[70]. The issue in

that case, however, was as to whether an abstract in a European patent application formed part of that application for the purposes of an issue as to added matter. I held that section 14(7) of the 1977 Act should be construed in the same sense as Article 85 EPC, and accordingly the abstract could not be taken into account. In my judgment this reasoning is not applicable to the present case, because PD2 is a United States patent application. Accordingly, neither section 14(7) nor Article 85 applied to it. Furthermore, section 5(1) of the 1977 Act should be construed consistently with Article 88(4) EPC and Article 4(H) of the Paris Convention, both of which provide that priority may be claimed where "the application documents as a whole" (to use the language of Article 4(H)) disclose the elements of the claim.

Assessment

131. Claims 1 and 2 of 689 and claims 1 and 6 of 122 can be considered together. The substantive features of claim 1 of each of the Patents are the same:

(a) zoledronate;

(b) for the treatment of osteoporosis;

(c) administered intravenously;

(d) at least about six months between administrations.

132. Claim 2 of 689 and claim 6 of 122 are as per claim 1, but require at least about a year between administrations.

133. The Claimants contend that these claims are not supported by the disclosure of PD2 for the following reasons. The skilled team will understand from PD2 that the intermittent administration of zoledronate will only be effective to treat osteoporosis (whether that is taken as increasing BMD or reducing fractures) at certain doses and at certain intervals. The subject matter of these claims, however, includes the intravenous administration of any dose of zoledronate at any interval greater than the specified minimum period. Furthermore, there is no disclosure in PD2 that zoledronate at any dosing regimen will be effective to cause a reduction in fractures in osteoporosis patients. All it discloses is that a particular dosing regimen causes an increase in BMD in a subset of osteoporosis patients. Accordingly, the subject matter of these claims extends well beyond the disclosure of PD2.

134. Novartis contend that these claims are supported by the disclosure of PD2 because, when read as a whole, the teaching of PD2 is that intravenous zoledronate at intervals of at least about six months is effective to treat osteoporosis.

135. For the reasons given above, I do not consider that these claims embrace the intravenous administration of *any* dose of zoledronate at *any* interval greater than the specified minimum period, but I do consider that they embrace any dose and any interval that works and that the skilled team would consider doses outside the range specified in claims 5 and 7 of 689 and intervals of 5-10 years or more to be potentially covered.

136. In my judgment PD2 does not disclose that intravenous zoledronate at intervals of at least about six months is effective to treat osteoporosis. My reasons are as follows.

137. First, PD2 begins by saying that the invention relates to bisphosphonates for the treatment of conditions of abnormally increased bone turnover (see paragraph 52 above). It then asserts that the inventors have found that bisphosphonates can be used for prolonged inhibition of bone resorption in conditions of abnormally increased bone turnover generally by intermittent administration at intervals of at least about 6 months (see paragraph 55 above). The skilled team would not read such a broad statement as a credible technical teaching, however. In any event, it is not a disclosure of the use of zoledronate to treat osteoporosis, let alone intravenously. It is true that PD2 goes on to identify zoledronate as one of the especially preferred bisphosphonates (see paragraph 58 above). It also identifies the treatment of osteoporosis as a particularly preferred embodiment (see paragraph 56 above). It also mentions intravenous administration as one of the preferred modes of administration (see paragraph 59 above). But nowhere in the general disclosure of PD2 (i.e. apart from Example 5) is any link made between zoledronate, osteoporosis, intravenous administration and administration at intervals of at least about six months. The nearest one gets is the abstract, which links zoledronate, osteoporosis and six monthly administration, but does not mention intravenous administration (see paragraph 70 above). As for Example 5, this is limited to the intravenous administration of particular doses of zoledronate to post-menopausal osteoporosis patients six monthly and yearly (see paragraphs 65-69 above).

138. Secondly, PD2 does not disclose that zoledronate will be effective to treat osteoporosis when administered intravenously at intervals of about 6 months or more regardless of dose. On the contrary, the skilled team would understand that whether it will do so or not will depend on the dosage used, the selection of which will in turn depend on various factors. Novartis suggested that the statement that "Normally the dosage is such that a single dosage of the bisphosphonate active ingredient from 0.005 – 0.20 mg/kg, esp. 0.01 – 10 mg/kg is administered" (see paragraph 60 above) was a teaching about dosages which applied across the scope of the PD2, and hence to the intravenous use of zoledronate to treat osteoporosis. But that is not correct: the document itself says, consistently with the skilled team's common general knowledge, that the dose used will depend on the bisphosphonate, the mode of administration and the condition in question (see paragraph 60 above). As Prof Russell agreed, the skilled person would not take this whole range as applying to any particular combination of bisphosphonate, mode of administration and condition.

139. Novartis also relied on the passage discussing unit doses of 1 – 10 mg, 1 – 5 mg and 2-10 mg (see paragraph 60 above). The problem with this is that there is nothing to indicate that it applies either to intravenous administration or to the treatment of osteoporosis. Prof Compston's view was that some of the range would be expected to be appropriate to intravenous administration while other parts would be appropriate to other modes of administration with lower bioavailabilities, such as transdermal. Prof Russell accepted that this passage was not stated to relate to intravenous administration and that there was nothing specific to indicate that it related to the treatment of osteoporosis. He said that it was "fairly obvious that those are the sort of doses which would be in play for intravenous administration", but that is far from

amounting to a disclosure that this range is effective to treat osteoporosis by intravenous administration.

140. Furthermore, this passage recommends a total dose over a period of 12 months of between 2 and 10 mg. The only teaching that the skilled person is given as to the dose and dosing interval which may be efficacious is in Example 5, which gives results only for a total dose of 4 mg per annum for the six and 12 month regimens. Prof Russell agreed that there was nothing in the Priority Document from which the skilled person could deduce that intravenous administration of zoledronate would be effective to increase BMD in osteoporosis patients using any dosing regimen other than those shown in Example 5 or, if so, over what range of doses.

141. Still further, Example 5 does not disclose that even 4 mg per annum zoledronate administered intravenously (whether in a single dose or in two six monthly doses) is effective to reduce fractures in osteoporosis patients. While the skilled team would agree with the statement that "A reduction of risk of osteoporotic fracture is expected" (see paragraph 69 above), the team would appreciate that a Phase 3 trial was required to confirm this. Thus there is no actual disclosure of efficacy in fracture reduction at any dose in PD2. More importantly, as Prof Russell accepted, the skilled person cannot tell from PD2 the range of doses at which zoledronate will be effective to reduce fractures in osteoporosis patients.

142. Claims 2 and 7 of 122 limit the condition to postmenopausal osteoporosis. The analysis set out above in relation to claims 1 and 6 of the 122 Patent is equally applicable to these claims.

143. Claim 5 of 689 has the following substantive features:

(a) zoledronate;

(b) for the treatment of osteoporosis;

(c) administered intravenously;

(d) in a unit dosage form of about 1-10 mg;

(e) at least about six months between administrations.

144. This combination is not disclosed in PD2 either. As discussed above, although PD2 discloses a unit dose form of 1-10 mg, this is not linked to the other features of the claim.

145. Claim 7 of 689 is as per claim 5, but with a unit dose of about 2-10 mg and a year between administrations. Again, this is not disclosed in PD2.

146. Accordingly, I conclude that none of the claims in issue is entitled to priority from PD2. (For completeness I would add that the Claimants had a separate priority attack on claim 17 of 122, but counsel for Novartis did not try to uphold the priority of that claim.) As stated above, Novartis has conceded that in those circumstances both Patents are invalid.

Boutsen

147. Boutsen is an abstract of a poster presented by Y. Boutsen, J. Jamart, W. Esselinckx and J.P. Devogelaer of the Departments of Rheumatology and Biostatisics, Mont-Godinne and St-Luc University (UCL) Hospitals, Belgium at the Second Joint Meeting of the American Society for Bone and Mineral Research and the International Bone and Mineral Society in San Francisco from 1-6 December 1998. It is abstract number T470 published along with some 2000 other abstracts in a Supplement to *Bone*, the Official Journal of the International Bone and Mineral Society, in November 1998.

148. Boutsen is sufficiently short to quote in full:

> "The aim of this study was to compare the efficacy of two regimens of intravenous pamidronate as primary prevention of glucocorticoid-induced osteoporosis (GIOP). At the time of initiating steroid therapy, 10 patients (Group A) received a single intravenous infusion of pamidronate (Aredia®, Novartis, Basle, Switzerland), 90 mg in 500 ml NaCl 0.9% over 2 hours; 10 patients (Group B) received a first infusion of 90 mg pamidronate and, subsequently, a 30-mg dose, in 250 ml NaCl 0.9% over 30 minutes every three months. As with control patients (Group C), they were all put on a daily 800-mg elemental calcium suppplement given as calcium carbonate. Patients were matched taking into account starting steroid doses, sex, menopausal status and hormonal replacement therapy. Lumbar spine and hip (total and subregions) bone mineral densities (BMDs) were measured at the start and at 6-monthly intervals by dual-energy X-ray absorptiometry (QDR-2000 Hologic, Inc.). Serum type I collagen fragments were measured using a one step ELISA method (CrossLaps®, Osteometer Biotech A/S Denmark) kindly analyzed by Claus Christiansen's group. Statistics were performed by ANOVA with repeated measurements. One patient (Group B) no longer required glucocorticoids after 3 months so that only 27 matched patients remained available for final analysis. After 1 year, cumulative steroid dosages expressed as mg prednisolone were respectively 3993 (2787) (Group A), 4962 (3300) (Group B) and 3162 (1425). BMD measurements at one year are expressed as % of initial values [mean(SD)] in the table.
>
> | | **Group A** | **Group B** | **Group C** |
> |---|---|---|---|
> | L1-L4 | 101.6 ± 2.1 | 102.2 ± 3.4 | 95.4 ± 2.8 |
> | Femoral neck | 101.2 ± 2.2 | 101.2 ± 2.3 | 96.8 ± 4.1 |
> | Total hip | 101.0 ± 3.5 | 102.6 ± 3.1 | 97.7 ± 2.2 |
>
> No difference was observed between pamidronate regimens but a highly significant difference was observed between both pamidronate regimens and the control group; $p<0.001$ at the

> lumbar spine; $p<0.01$ at the femoral neck and $p<0.05$ at the total hip. Serum CrossLaps demonstrated a progressive decrease in all groups during the first six months, more marked after 3 months in groups A and B. A sustained decrease was only observed throughout in group B. As far as BMD evolution over one year is concerned, intravenous pamidronate given as a single infusion or on a three-monthly regimen effectively achieved primary prevention of glucocorticoid-induced osteoporosis."

149. It is convenient to note at this point that the poster of which Boutsen is an abstract is not a great deal longer, but it does contain some more information. In particular, it contains a table of alkaline phosphatase and CrossLaps (CTX) measurements for patients who received (a) calcium, (b) a single infusion of pamidronate and (c) three-monthly pamidronate and graphs plotting these data against time. It can be seen from the table and the graphs that (i) there are no data points at 6 or 9 months and (ii) at 12 months the CTX level has returned to close to baseline in the single infusion group whereas the CTX level in the three-monthly group remains significantly below baseline. (In the case of the single infusion group, the mean figure for CTX is 2/3 of baseline, but the standard deviation is so large that it appears unlikely that the result is statistically significantly different.)

150. It is also convenient to note that Boutsen *et al* subsequently published a full paper on this study, "Primary Prevention of Glucocorticoid-Induced Osteoporosis with Intravenous Pamidronate and Calcium: A Prospective Controlled 1-Year Study Comparing a Single Infusion, an Infusion Given Once Every 3 Months and Calcium Alone", *J. Bone & Min. Res.* 16(1), 104-112 (2001). This was after the priority date, however.

Obviousness

The law

151. The familiar structured approach to the assessment of allegations of obviousness first articulated by the Court of Appeal in *Windsurfing International Inc v Tabur Marine (Great Britain) Ltd* [1985] RPC 59 was re-stated by Jacob LJ in *Pozzoli v BDMO SA* [2007] EWCA Civ 588, [2007] FSR 37 at [23] as follows:

> "(1)(a) Identify the notional 'person skilled in the art';
>
> (b) Identify the relevant common general knowledge of that person;
>
> (2) Identify the inventive concept of the claim in question or if that cannot readily be done, construe it;
>
> (3) Identify what, if any, differences exist between the matter cited as forming part of the 'state of the art' and the inventive concept of the claim or the claim as construed;

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

152. The correct approach to the fourth step in a case such as the present was recently summarised by Kitchin LJ, with whom Lewison and Moore-Bick LJJ agreed, in *MedImmune Ltd v Novartis Pharmaceuticals Ltd* [2012] EWCA Civ 1234 as follows:

> "90. One of the matters which it may be appropriate to take into account is whether it was obvious to try a particular route to an improved product or process. There may be no certainty of success but the skilled person might nevertheless assess the prospects of success as being sufficient to warrant a trial. In some circumstances this may be sufficient to render an invention obvious. On the other hand, there are areas of technology such as pharmaceuticals and biotechnology which are heavily dependent on research, and where workers are faced with many possible avenues to explore but have little idea if any one of them will prove fruitful. Nevertheless they do pursue them in the hope that they will find new and useful products. They plainly would not carry out this work if the prospects of success were so low as not to make them worthwhile. But denial of patent protection in all such cases would act as a significant deterrent to research.
>
> 91. For these reasons, the judgments of the courts in England and Wales and of the Boards of Appeal of the EPO often reveal an enquiry by the tribunal into whether it was obvious to pursue a particular approach with a reasonable or fair expectation of success as opposed to a hope to succeed. Whether a route has a reasonable or fair prospect of success will depend upon all the circumstances including an ability rationally to predict a successful outcome, how long the project may take, the extent to which the field is unexplored, the complexity or otherwise of any necessary experiments, whether such experiments can be performed by routine means and whether the skilled person will have to make a series of correct decisions along the way. Lord Hoffmann summarised the position in this way in *Conor* at [42]:
>
> > 'In the Court of Appeal, Jacob LJ dealt comprehensively with the question of when an invention could be considered obvious on the ground that it was obvious to try. He correctly summarised the authorities, starting with the judgment of Diplock LJ in *Johns-Manville Corporation's Patent* [1967] RPC 479, by saying that the notion of something being obvious to try was useful only in a case where there was a fair expectation of success. How much of an expectation

> would be needed depended on the particular facts of the case.'

92. Moreover, whether a route is obvious to try is only one of many considerations which it may be appropriate for the court to take into account. In *Generics (UK) Ltd v H Lundbeck*, [2008] EWCA Civ 311, [2008] RPC 19, at [24] and in *Conor* [2008] UKHL 49, [2008] RPC 28 at [42], Lord Hoffmann approved this statement of principle which I made at first instance in *Lundbeck*:

> 'The question of obviousness must be considered on the facts of each case. The court must consider the weight to be attached to any particular factor in the light of all the relevant circumstances. These may include such matters as the motive to find a solution to the problem the patent addresses, the number and extent of the possible avenues of research, the effort involved in pursuing them and the expectation of success.'

93. Ultimately the court has to evaluate all the relevant circumstances in order to answer a single and relatively simple question of fact: was it obvious to the skilled but unimaginative addressee to make a product or carry out a process falling within the claim…."

153. The primary evidence as to obviousness is that of properly qualified experts and secondary evidence needs to be kept in its place: see *Mölnlycke AB v Procter & Gamble Ltd* [1994] RPC 49 at 112-114 (Sir Donald Nicholls V-C). Nevertheless there are cases in which secondary evidence is important: see *Schlumberger Holdings Ltd v Electromagnetic Geoservices AS* [2010] EWCA Civ 819, [2010] RPC 33 at [76]-[85] (Jacob LJ).

154. In assessing whether a claimed invention is obvious, it is always important, although difficult, to avoid hindsight. The fact that, after the event, it is easy to see how the invention could be arrived at by starting from an item of prior art and taking a series of apparently simple steps does not necessarily show that it was obvious at the time: *British Westinghouse Electric & Manufacturing Co Ltd v Braulik* (1910) 27 RPC 209 at 230 (Fletcher Moulton LJ), *Non-Drip Measure Co Ltd v Strangers Ltd* (1943) 60 RPC 135 at 142 (Lord Russell) and *Technograph Printed Circuits Ltd v Mills & Rockley (Electronics) Ltd* [1972] RPC 346 at 362 (Lord Diplock).

The skilled team and the common general knowledge

155. I have identified these above.

The inventive concept

156. As indicated above, the inventive concept of claim 1 of each of the patents is the same: the use of zoledronate for the treatment of osteoporosis administered

intravenously with at least about six months between administrations. Although Novartis' formal position is that it contends that claims 2, 5 and 7 of 689 and claims 2, 6 and 7 of 122 are independently valid over Boutsen, counsel for Novartis did not advance any argument to support the independent validity of those claims in his closing submissions.

The difference

157. Counsel for Novartis submitted that there were three differences between Boutsen and the claimed inventions:

i) Boutsen was concerned with pamidronate, not zoledronate.

ii) Boutsen did not disclose intravenous administration at intervals of at least about six months.

iii) Boutsen did not disclose that intravenous administration at intervals of at least about six months was effective in the treatment of osteoporosis.

158. Counsel for the Claimants accepted the first difference, but took issue with the other two. In my view he was correct to do so. While it is true to say that Boutsen does not disclose repeated administration of pamidronate to the group which received a single infusion in the 12 month study period, the same is true of Example 5 in the Patents. In both cases the clear implication is that administration can then be repeated to cover further 12 month periods. As for efficacy, both Boutsen and Example 5 of the Patents disclose a statistically significant increase in BMD. In both cases the skilled team would accept that as predictive of a reduced fracture risk, although in both cases confirmation would require a Phase 3 trial with fracture rate as the primary endpoint.

Was the step obvious?

159. As is frequently the case, it is convenient to break the analysis down into a series of smaller questions before drawing an overall conclusion.

160. *The context in which Boutsen is taken to be read*. The Claimants' primary case on obviousness is based on the assumption that the skilled team has already decided to undertake a Phase 2 clinical trial of zoledronate administered intravenously for the treatment of osteoporosis and then has Boutsen put in front of them. Counsel for Novartis submitted that this assumption was illegitimate, since it involved hindsight. Rather, the context in which the skilled team should be taken to read Boutsen is that they are looking to improve the existing bisphosphonate treatments for osteoporosis, but have not yet decided what avenue to pursue. I agree with this.

161. *Would the skilled team obtain the poster?* Both Prof Compston and Prof Russell were of the view that the skilled team would want to see the poster of which Boutsen was the abstract. In my judgment obtaining a copy of the poster would be an entirely obvious step to take. Counsel for the Claimants pointed out in his closing submissions that Novartis, who had put the poster in evidence, had not proved that it would be possible for the skilled team to obtain a copy of the poster. He did not put to Prof Russell any reason why there would be a problem in doing so, however, nor did he

suggest any such reason in his submissions. I consider it probable that the skilled team would have been able to obtain a copy of the poster by contacting the authors.

162. *Would the skilled team put Boutsen on one side?* Novartis contends that the skilled team, having read Boutsen properly, would put it on one side as not being of any assistance in addressing the problem identified above. I do not accept this. This proposition was not advanced by Prof Russell in any of his evidence, nor was it put to Prof Compston.

163. *What would the skilled team take from Boutsen?* In the alternative to the preceding contention, Novartis contends that the skilled team would not regard Boutsen as encouraging them to try a Phase 2 trial of pamidronate for the treatment of osteoporosis administered intravenously at either six or 12 monthly intervals, let alone zoledronate. Novartis advances a number of reasons for this, which I shall consider in turn.

164. First, Boutsen is only an abstract, only one of many and not peer reviewed. I am unimpressed with these points. So far as the first is concerned, I have already held that the skilled team would obtain the poster; but it is legally irrelevant anyway. The second point is also legally irrelevant. I accept that the skilled team would take into account the fact that the abstract had not been peer-reviewed, but on the other hand Prof Russell accepted that it was from a respected group. Accordingly, the skilled team would assess Boutsen on its merits.

165. Secondly, there is the small number of patients in the study, namely nine per group. Prof Russell laid some emphasis on this point, but he nevertheless accepted that there were enough patients for the authors to be able to draw statistically significant conclusions from the BMD data.

166. Thirdly and most importantly, the skilled team would regard the bone resorption marker data reported in Boutsen as more relevant for the purposes of assessing an appropriate dosage regime than the BMD data. Boutsen itself states that "A sustained decrease [in CTX] was only observed in Group B [i.e. the three monthly group]". This becomes even clearer if one looks at the data and graph in the poster. Prof Russell considered that the skilled team would be very concerned by this, and would be deterred from administering pamidronate at 12 monthly intervals. Prof Compston placed more weight on the BMD data. She also pointed out that the three monthly group had received a higher total dose over the 12 month period and emphasised the absence of CTX data at six and nine months.

167. Having regard to my conclusion as to the common general knowledge of the skilled team, I consider that the skilled team would be influenced by the marker data. The BMD data are positive for both the single infusion group and the three monthly group, but they are more positive for the three monthly group. The difference does not appear to be statistically significant, but it is noticeably greater in the case of the total hip measurements. The marker data are clearly more positive for the three monthly group than the single infusion. In the absence of the marker data at six and nine months, it is very difficult to know how much weight to give to the fact that the three monthly group received a higher total dose. In these circumstances, I consider that the skilled team would have a reasonable expectation that a Phase 2 trial of pamidronate administered intravenously at three monthly intervals would be successful, but would

be rather more cautious about whether administration at 12 monthly intervals would be successful. In particular, they would recognise that success might well depend on selection of the appropriate dose.

168. I would add that I do not think that Boutsen would suggest to the skilled team that pamidronate should be administered at six monthly intervals. To begin with, Boutsen *et al* did not study this. Although Boutsen states that the CTX data "demonstrated a progressive decrease in all groups during the first six months", that includes the calcium only group. Furthermore, the poster indicates that this statement is based on extrapolation: there are in fact no data at six months.

169. *Would the skilled team regard Boutsen's teaching as applicable to zoledronate?* Having regard to my conclusions as to the skilled team's common general knowledge, I consider that the skilled team would regard Boutsen's teaching as of relevance to other bisphosphonates, including zoledronate, but they would not assume that it could be simply translated to zoledronate. In particular, they would realise that, both because of the uncertainty over the influence of the total dose in Boutsen itself and because of the difference between zoledronate and pamidronate, Boutsen provides little guidance as to the appropriate dose of zoledronate to use.

170. *What dose of zoledronate would the skilled team contemplate using in a Phase 2 trial?* The Claimants contend that it would be obvious for a skilled team considering a Phase 2 trial of zoledronate for the treatment of osteoporosis to do a literature search to find out what doses of zoledronate had been used in previous studies and that such a search would have turned up at least an article by Sorbera *et al*, "Zoledronate Disodium: Treatment of Tumor-Induced Hypercalcemia, Angiogenesis Inhibitor", *Drugs of the Future* 25(3): 259-268 (2000) which summarises a number of studies. I accept this submission, which is supported by the evidence of Prof Russell in cross-examination.

171. The Claimants rely on the fact that Sorbera reports two Phase 2 trials of zoledronate. The information is reported in two different places on the same page, and there are some inconsistencies between the passages, but the upshot appears to be as follows. In the first trial 0.4 mg, 2 mg and 4mg zoledronate was administered intravenously monthly to patients with osteolytic bone metastases for nine months and compared to 90 mg pamidronate administered intravenously monthly. In the second trial the same doses of zoledronate and pamidronate were administered at the same intervals for the same period to cancer patients with osteolytic lesions. In at least the second trial the efficacy of 4 mg zoledronate was found to be comparable to that of 90 mg pamidronate, and the results of the first trial appear to have been similar.

172. There is little evidence as to what the skilled team would make of this information. The Claimants adduced no evidence from Prof Compston on the point, and the matter was not fully explored with Prof Russell in cross-examination. Nevertheless I agree with the Claimants that a skilled team considering a Phase 2 trial of zoledronate administered intravenously for the treatment of osteoporosis would take the doses reported in Sorbera as a starting point. Having regard to my conclusions as to the skilled team's common general knowledge, however, I do not consider that they would think that they could simply translate the doses reported in Sobera to the context of osteoporosis treatment and expect success. Still less would the skilled team

think that they could simply substitute a single infusion of 4 mg of zoledronate for 90 mg of pamidronate in Boutsen and expect success.

173. *The motive to find a solution to the problem*. I do not understand there to be any dispute that the skilled team would be motivated to find a better bisphosphonate treatment for osteoporosis. There was a need for improved treatments, and in particular there was a need for treatments which addressed the problems associated with orally administered etidronate and alendronate. Furthermore, the incidence of post-menopausal osteoporosis meant that this was an important issue to be addressed.

174. *Other avenues of research.* It was common ground between Prof Compston and Prof Russell that in June 2000 a number of other avenues of research were being pursued in addition to investigating alternative dosing regimens. These included:

i) developing new bisphosphonate molecules;

ii) developing prodrugs of existing bisphosphonates;

iii) using existing bisphosphonates for alternative conditions;

iv) investigating different formulations;

v) investigating combinations of existing drugs; and

vi) investigating different routes of administration.

175. Some of these, such as the first two, I do not regard as particularly realistic alternatives for a skilled team starting from Boutsen, but others are.

176. *The effort required*. The Claimants contend that it would not take the skilled team a great deal of effort to design and carry out a Phase 2 trial of intravenous zoledronate for the treatment of osteoporosis with three monthly, six monthly and 12 monthly arms. Novartis counters that this would take a great deal more effort than, say, a simple *in vitro* test. In my view the skilled team would regard the effort as not inconsiderable, particularly bearing in mind the need to include a range of doses, and would only undertake it if satisfied that the prospect of success was sufficient.

177. *The prospects of success*. Would the skilled team, having read Boutsen, have concluded that intravenous zoledronate at six monthly or 12 monthly intervals for the treatment of osteoporosis was likely to be successful (by which I mean sufficiently successful in terms of BMD increase and bone resorption marker suppression to justify a Phase 3 trial to confirm fracture risk reduction)? Prof Russell was firmly of the opinion that they would not have done. Prof Compston was of the opinion that they would. Having regard to my findings as to the skilled team's common general knowledge and the answers to previous questions that I have given, I conclude that the skilled team would have regarded the prospects of success as highly uncertain.

178. *Secondary evidence*. Novartis relies strongly on two strands of secondary evidence as showing that the claimed inventions were not obvious. First, the Example 5 Phase 2 trial was subsequently fully reported in Reid *et al*, "Intravenous Zoledronic Acid in Postmenopausal Women with Low Bone Mineral Density", *N. Eng. J. Med.* 346(9): 653-661 (2002). Prof Russell was one of the peer reviewers of this paper. In his

comments to the editors, he strongly recommended acceptance "on the grounds that it represents a landmark advance in the field and could revolutionise the management of osteoporosis". In his remarks for the authors, he commented that the reason why a single dose of 4 mg zoledronate should suppress bone turnover for a whole year "remains a fascinating mystery". At the time he wrote this, Prof Russell was not aware of Boutsen, but his evidence was that he would have expressed the same views if he had been.

179. Secondly, Prof Compston and a colleague contributed a chapter entitled "The future diagnosis and management of osteoporosis" to a book entitled *Bone and Joint Futures* edited by Anthony Woolf which was published in 2002. It is likely that the chapter was written in 2000 or at latest in 2001. Prof Compston was aware of Boutsen at the time, yet in speculating as to future developments in the treatment of osteoporosis she did not predict intravenous administration of bisphosphonates at intervals of six months or more. Rather, she contemplated three-monthly administration.

180. Both Prof Russell and Prof Compston were leaders in the field, but that enhances, rather than detracts from, the value of this evidence from Novartis' perspective. In my view these points provide some modest support for a conclusion of non-obviousness, but no more than that.

181. *Overall conclusion.* As the Court of Appeal has repeatedly emphasised, it is important not to lose sight of the fact that in the end the court is faced with a single question: would it have been obvious to the skilled team to take the step from Boutsen to the claimed invention or not? Taking all of the factors considered above into account, my conclusion is that it would not have been obvious.

Insufficiency

182. The Claimants contend that the open-ended claims of the Patents, i.e. claims 1, 2 and 5 of 689 and claims 1, 2, 6 and 7 of 122, are invalid for insufficiency because they are not enabled across their breadth. I reviewed the law of insufficiency at some length in *MedImmune Ltd v Novartis Pharmaceuticals UK Ltd* [2011] EWHC 1699 (Pat) at [458]-[484] and *Sandvik Intellectual Property AB v Kennametal UK Ltd* [2011] EWHC 3311 (Pat), [2012] RPC 23 at [106]-[124]. For the purposes of the present case it is sufficient to cite Jacob LJ's pithy summary in *Novartis AG v Johnson & Johnson Medical* Ltd [2010] EWCA Civ 1039, [2011] ECC 10 at [74]:

> "The heart of the test is: 'Can the skilled person readily perform the invention over the whole area claimed without undue burden and without needing inventive skill?'"

On the facts, he agreed with counsel for Johnson & Johnson at [77] that the patent in suit "did no more than invite the reader to perform a research program where, if he succeeded, the patent claimed the fruits of his research".

183. In the present case, it is inherently unlikely that zoledronate will treat osteoporosis regardless of how low the dose is and how long the dosing interval is. Prof Russell stated in his first report that it would not present any difficulty to the skilled team to work out from the information given in the specification and the common general knowledge, the dosage level that would be appropriate and the frequency of dosage

administration. In cross-examination, he explained that what he meant by that was that the skilled team could choose a suitable dose and dosage interval for post-menopausal osteoporosis patients to use for a Phase 3 study to test for efficacy in fracture reduction.

184. Counsel for the Claimants submitted that this evidence did not assist Novartis because the Patents claimed the use of any zoledronate dose and dosage interval to treat osteoporosis when it was clear that not all doses and dosage intervals claimed will be effective. Counsel for Novartis riposted that the claims did not extend to any dose and any dosage interval, but only to those which worked.

185. As I have said, I agree with counsel for Novartis that the claims in issue should not be interpreted as extending to any dose and any dosage interval. But they do extend to any dose and any dosage interval which works. Furthermore, their potential scope is quite broad. In my judgment the claims are not enabled across their breadth because they place an undue burden on the skilled team to find out what doses and dosage intervals work. To confirm that 4 mg once yearly, the regimen used in Example 5, is effective in reducing fractures in post-menopausal osteoporosis patients, one needs to do a Phase 3 trial, which takes considerable effort and time (not to mention money). But to determine whether other doses and/or other dosage intervals are effective in that or other patient groups is very onerous. Prof Russell accepted that this was something that the skilled team was left to find out for themselves. The kind of work involved can be illustrated by a study in HIV-infected men mentioned by Prof Russell, which involved two 4 mg annual administrations of zoledronate plus five years follow up. This study only measured BMD and bone turnover markers, and yet larger studies were proposed to assess the anti-fracture effect. That is for just one dosing regimen in one group of patients.

186. In short, the claims in issue require the skilled team to carry out a substantial program of clinical trials to find out what doses and dosing intervals are efficacious, and then claim the results. Accordingly they are invalid for insufficiency.

Summary of conclusions

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

i) None of the claims is entitled to priority from PD2. It follows that both Patents are invalid.

ii) None of the claims is obvious over Boutsen.

iii) Claims 1, 2 and 5 of 689 and claims 1, 2, 6 and 7 of 122 are invalid for insufficiency.