# EXHIBIT C
# (part 2 of 3)

# EXHIBIT A

| U.S. PATENT NO. 5,441,868 CLAIM 1 | | |
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| **Claim Limitations** | **Proposed Claim Construction** | **Corresponding Step in Roche's Production Process** |
| A process for the production of a glycosylated erythropoietin polypeptide | **"A process for the production of an erythropoietin polypeptide having one or more carbohydrate groups attached to the polypeptide"** | **Roche uses the recited process to produce the glycosylated erythropoietin polypeptide in RO0503821.**<br><br>"Both EPO starting material and RO0503821 have the identical amino acid sequence and composition of the carbohydrate moiety. RO0503821 differs from erythropoietin through integration of an amide bond between wither the N-terminal amino group of the ε-amino group of lysine, predominantly Lys 52 and Lys 45 and methoxy polyethylene glycol-succinimidyl butanoic acid. This results in a molecular weight of around 60 kDa." ITC-R-BLA-00004027<br><br>"Ro 50-3821 and epoetin beta share an identical amino acid sequence and composition. The only difference in the composition of native and modified protein is due to the formation of an amide bond between the amino group of epoetin beta and the methoxy-PEG molecule at the point of attachment." ITC-R-IND-00000979.<br><br>"Both EPO and Ro 50-3821 have identical amino acid sequence and composition of the carbohydrate moiety. The only difference in the composition of native and modified protein is due to the formation of an amide bond between the amino group of EPO and the PEG molecule at the point of attachment." ITC-R-00050548.<br><br>"For all batches of RO0503821, Epoetin beta, the active ingredient of the medicinal product Recormon®/NeoRecormon® was used as a starting |

| U.S. PATENT NO. 5,756,349 CLAIM 1 | | |
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| **Claim Limitations** | **Proposed Claim Construction** | **Corresponding Structure or Function in Roche's Vertebrate Cells** |
| | | use a mammalian vector/host expression system. The advantages of the system selected (gene amplification in Chinese hamster ovary (CHO) cells) are that the protein is folded, disulfide linked, glycosylated, and secreted into the growth medium." ITC-R-BLA-00004803.<br><br>"Compositions of the Media." ITC-R-BLA-00004674-4676.<br><br>"EPO is produced in suspension culture in an 1,000 L bioreactor scale in a production process without using animal and human derived raw materials." ITC-R-00076656. |
| which are capable upon growth in culture of producing erythropoietin in the medium of their growth in excess of 100 U of erythropoietin per $10^6$ cells in 48 hours as determined by radioimmunoassay, | **"[the vertebrate cells] are able to secrete erythropoietin into their growth environment in excess of 100 U of erythropoietin per $10^6$ cells in 48 hours as determined by radioimmunoassay"** | **The erythropoietin in RO0503821 is made using vertebrate cells which are capable upon growth in culture of producing erythropoietin in the medium of their growth in excess of 100U of EPO per $10^6$ cells in 48 hours as determined by radioimmunoassay.**<br><br>**-- "producing erythropoietin in the medium of their grown"**<br><br>"Epoetin beta (EPO) is produced by the recombinant CHO cell line DN2-3 α 3 in suspension culture." ITC-R-BLA-00004667<br><br>"Compositions of the Media." ITC-R-BLA-00004674-4676.<br><br>"In order to produce a recombinant EPO with properties similar to the natural EPO, Genetics Institute decided to use a mammalian vector/host expression system. The advantages of the system selected (gene amplification in Chinese hamster ovary (CHO) cells) are that the protein is folded, disulfide linked, glycosylated, and secreted into the |

| U.S. PATENT NO. 5,756,349 CLAIM 1 | | |
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| **Claim Limitations** | **Proposed Claim Construction** | **Corresponding Structure or Function in Roche's Vertebrate Cells** |
| | | growth medium." ITC-R-BLA-00004803.<br>**--"growth in excess of 100 U [or 1000 U] of erythropoietin per $10^6$ cells in 48 hours as determined by radioimmunoassay"**<br>*See, e.g.*, ITC-BLA-00002375-2378<br>*See Amgen v. Chugai* Trial Exhibits PX809 (Chugai's IND Vol. 1.1) at A140432 (Table 4.2.4-2), A140345, and A140416; and PX 19 (Chugai's IND at A119857-69, A119870, A120069-A12088).<br>"As a basis for its denial, Roche directs Amgen to the MIRCERA™ BLA, in which Roche admits that "[t]he periods for the fermentation phases are specified to achieve the specified cell densities and product yield. The product yield is controlled by the determination of product concentration and harvest volume." ITC-R-BLA-00005170." Roche's Response to Request for Admission No. 21. |
| said cells comprising non-human DNA sequences which control transcription of DNA encoding human erythropoietin. | **"said cells containing at least DNA sequences, which are not part of the human genome, but which initiate and regulate the process of transcription of the genetic instructions for human erythropoietin"** | **The erythropoietin in RO0503821 is made using vertebrate cells that contain non-human DNA sequences which control transcription of DNA encoding human erythropoietin.**<br>**Roche's DN2-3α3 cells contain non-human DNA sequences (the adenovirus type 2 major late promoter).**<br>"The vector contains four known promoters that could be functional in mammalian cells. The expression of the inserted [EPO] cDNA is driven by the adenovirus type 2 major late promoter found in fragment 6." ITC-R-BLA-00004804. |

| U.S. PATENT NO. 5,756,349 CLAIM 1 | | |
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| **Claim Limitations** | **Proposed Claim Construction** | **Corresponding Structure or Function in Roche's Vertebrate Cells** |
| | | "Roche directs Amgen to the MIRCERA™ BLA, in which Roche admits that "[t]he [expression] vector contains four known promoters that could be functional in mammalian cells. . . . It is possible that some of the EPO mRNA in the expressing DN2-3α3 line is derived from transcription initiating at the SV40 early promoter in fragment 5." ITC-R-BLA-00004804." Roche's Response to Request for Admission No. 20.<br><br>**The adenovirus type 2 major later promoter in Roche's DN2-3α3 cells controls transcription of DNA encoding human erythropoietin.**<br>"The Epoetin beta (EPO) coding sequence was introduced into CHO cells deficient in the enzyme dihydrofolate reductase (DHFR) by transformation with a linked mouse DHFR, and selection for the DHFR phenotype." ITC-R-BLA-00004934.<br><br>"High level expression of EPO was achieved by transformation of the DHFR-CHO cells with a vector expressing both EPO and DHFR cDNAs, and subsequent gene amplification by selection in increasing levels of the DHFR inhibitor methotrexate (MTX, and inhibitor of DHFR)." ITC-R-BLA-00004723.<br><br>"The expression vector for EPO was chosen considering that it should be able to express the cDNA in a CHO cell." ITC-R-BLA-00004723.<br><br>"As a basis for its denial, Roche directs Amgen to the MIRCERA™ BLA, in which Roche admits that "[t]he EPO coding sequence was introduced into CHO cells deficient in the enzyme DHFR by transformation with a |

| U.S. PATENT NO. 5,756,349 CLAIM 1 | | |
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| **Claim Limitations** | **Proposed Claim Construction** | **Corresponding Structure or Function in Roche's Vertebrate Cells** |
| | | linked mouse DHFR cDNA, and selection for the DHFR' phenotype." ITC-R-BLA-00004723." Roche's Response to Request for Admission No. 18.<br><br>"As a basis for its denial, Roche directs Amgen to the MIRCERA™ BLA, in which Roche admits that "[t]he Epoetin beta (EPO) coding sequence was introduced into CHO cells deficient in the enzyme dihydrofolate reductase (DHFR) by transformation with a linked mouse DHFR cDNA and selection for the $DHFR^+$ phenotype. Upon further selection with increasing levels of the drug methotrexate (MTX, an inhibitor of DHFR), the co-integrated DHFR and EPO sequences were amplified to high copy number." ITC-R-BLA-00004987." Roche's Response to Request for Admission No. 19.<br><br>*See also* ITC-R-BLA-00004722-4727. |

| U.S. PATENT NO. 5,547,933 CLAIM 3 | | |
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| **Claim Limitations** | **Proposed Claim Construction** | **Corresponding Structure or Function in Roche's Product** |
| A non-naturally occurring glycoprotein product of the expression in a mammalian host cell of an exogenous DNA | **"a protein not occurring in nature having carbohydrate groups attached to the polypeptide that is produced by a mammalian cell from DNA transformed or transfected into the mammalian cell that does not have its origin from the genome of** | **RO0503821 contains a non-naturally occurring glycoprotein product.**<br><br>"Ro 50-3821 is a synthetic human erythropoietin, epoetin beta, produced by recombinant DNA technology which is then modified by chemically conjugating one linear |

| U.S. PATENT NO. 5,547,933 CLAIM 3 | | |
|---|---|---|
| **Claim Limitations** | **Proposed Claim Construction** | **Corresponding Structure or Function in Roche's Product** |
| sequence comprising | **the host"** | methoxy-polyethylene glycol molecule to its N-terminus or lysine residue." ITC-R-IND-000000542.<br><br>"Epoetin beta is a synthetic glycoprotein produced by recombinant DNA technology in Chinese hamster ovarian (CHO) cells." ITC-R-IND-000000979.<br><br>"The experimental drug used in this study, Ro 50-3821 is a new compound, which is similar to the human hormone erythropoietin. Like currently available drugs called epoetins, Ro 50-3821 can increase the number of red blood cells and hemoglobin levels in the blood. Ro 50-3821 is also produced by genetic engineering techniques, but the drug is manufactured in such a way that to the drug [sic] can stay in the body's circulation for a long time." ITC-R-IND-00000771.<br><br>"RO0503821 is comprised of human epoetin beta (EPO, Ro 205-3859), which is mono-peglated with a linear methoxy-polyethlene glcol (PEG), with an average molecular weight of around 30 kDa. RO0503821 is the reaction product of EPO and methoxy-polyethlene glycol-succinimidyl butyric acid (Ro 50-3919).<br>The only difference in the composition of native and modified protein is due to the formation of an amide bond between the amino group of EPO and the PEG molecule at the point of attachment." ITC-R-00076642<br><br>"Ro 50-3821 and epoetin beta share an identical amino acid sequence and composition. The only difference in the composition of native and modified protein is due to the formation of an amide bond between the amino group of epoetin beta and the methoxy-PEG molecule at the point of |

| U.S. PATENT NO. 5,547,933 CLAIM 3 | | |
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| **Claim Limitations** | **Proposed Claim Construction** | **Corresponding Structure or Function in Roche's Product** |
| | | attachment." ITC-R-IND-00000979.<br><br>"For all batches of RO0503821, Epoetin beta, the active ingredient of the medicinal product Recormon®/NeoRecormon® was used as a starting material. Epoetin beta, a recombinant erythropoietin, is manufactured at Roche Pharma Biotechnology Production in Penzberg, Germany.<br>The EPO starting material remained unchanged during the process development of RO0503821." ITC-R-BLA-00004178.<br><br>"[I]t was demonstrated by means of extended characterization using different analytical methods that apart from slight quantitative differences, the carbohydrate structure of RO0503821 remains unchanged as compared to EPO starting material." ITC-R-BLA-00004317.<br><br>"Figure 14 compares the relative contents of the different structures found in Ro 50-3821 and unmodified EPO. All oligosaccharide structures known from unmodified recombinant EPO are also present in Ro 50-3821. The chromatogram provides no evidence for altered oligosaccharide structures after pegylation of EPO (see Figure 13)." Comparability Program for Ro 50-3821 Drug Substance 5/21/03, p. 1-69 ITC-R-00090941, at 91008<br><br>"Figure 9 compares the relative contents of the different structures found in pegylated EPO and unmodified EPO. All oligosaccharide structures knowen from unmodified EPO are also present in Ro 50-3821. The chromatogram provides no evidence for altered oligosaccharide structures after pegylation of EPO (see figure 8). From a quantitative |

| U.S. PATENT NO. 5,547,933 CLAIM 3 | | |
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| **Claim Limitations** | **Proposed Claim Construction** | **Corresponding Structure or Function in Roche's Product** |
| | | point of view small differences could be seen in the oligosaccharide pattern between pegylated EPO and unmodified EPO (see figure 9)." ITC-R-IND-00005504-5531, at 5521.<br><br>"PEG-EPO (Ro 50-3821) is comprised of human epoetin beta (Ro 205-3859), which is mono-pegylated with a linear methoxy-polyethylene glycol (PEG) with an average molecular weight of 32 kDa. PEG-EPO consists of at least 90% mono-pegylated EPO and the remainder is comprised of di-pegylated EPO, higher pegylated EPO and non-pegylated EPO (less than 1%)." ITC-R-00050625<br><br>"PEG-EPO (Ro 50-3821) is a pegylated version of Epoetin beta, whereby one linear polyethylene glycol chain has been added to the recombinant erythropoietin molecule." ITC-R-IND-00070631.<br><br>*See also* ITC-R-BLA-00006908; ITC-R-BLA-00013120 at 00013131; Farid Depo. Tr. 184:22-185:7, ITC-R-00076640; ITC-R-BLA-00019133 at 19136; ITC-R-BLA-00000005 at 00006287; ITC-R-BLA-00018966 at 18969; ITC-R-BLA-00016194 at 00016202; ITC-R-BLA-00016096 at 00016104; ITC-R-IND-00062646; ITC-R-IND-00000542; ITC-R-BLA-00007319 at 00007349; ITC-R-BLA-00002509 at 00002525; ITC-R-00076642; ITC-R-BLA-00004027; ITC-R-IND-00000542; ITC-R-IND-00000979; Application Summary for MIRCERA, ITC-R-BLA-00000194-691; Drug Substance – RO0503821, ITC-R-BLA-00004024-4650.<br><br>**The glycoprotein product in RO0503821is the product of the expression in a mammalian host cell of an** |

| U.S. PATENT NO. 5,547,933 CLAIM 3 | | |
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| **Claim Limitations** | **Proposed Claim Construction** | **Corresponding Structure or Function in Roche's Product** |
| | | **exogenous DNA sequence.**<br><br>"The Epoetin beta (EPO) coding sequence was introduced into CHO cells deficient in the enzyme dihydrofolate reductase (DHFR) by transformation with a linked mouse DHFR, and selection for the DHFR phenotype." ITC-R-BLA-00004934.<br><br>"High level expression of EPO was achieved by transformation of the DHFR-CHO cells with a vector expressing both EPO and DHFR cDNAs, and subsequent gene amplification by selection in increasing levels of the DHFR inhibitor methotrexate (MTX, and inhibitor of DHFR)." ITC-R-BLA-00004723.<br><br>"In order to produce a recombinant EPO with properties similar to the natural EPO, Genetics Institute decided to use a mammalian vector/host expression system. The advantages of the system selected (gene amplification in Chinese hamster ovary (CHO) cells) are that the protein is folded, disulfide linked, glycosylated, and secreted into the growth medium." ITC-R-BLA-00004803.<br><br>"The expression vector for EPO was chosen considering that it should be able to express the cDNA in a CHO cell." ITC-R-BLA-00004723.<br><br>"As a basis for its denial, Roche directs Amgen to the MIRCERA™ BLA, in which Roche admits that "[t]he EPO coding sequence was introduced into CHO cells deficient in the enzyme DHFR by transformation with a linked mouse DHFR cDNA, and selection for the DHFR' phenotype." ITC-R-BLA-00004723." Roche's Response to Request for Admission No. 18. |

| U.S. PATENT NO. 5,547,933 CLAIM 3 | | |
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| **Claim Limitations** | **Proposed Claim Construction** | **Corresponding Structure or Function in Roche's Product** |
| | | "As a basis for its denial, Roche directs Amgen to the MIRCERA™ BLA, in which Roche admits that "[t]he Epoetin beta (EPO) coding sequence was introduced into CHO cells deficient in the enzyme dihydrofolate reductase (DHFR) by transformation with a linked mouse DHFR cDNA and selection for the $DHFR^+$ phenotype. Upon further selection with increasing levels of the drug methotrexate (MTX, an inhibitor of DHFR), the co-integrated DHFR and EPO sequences were amplified to high copy number." ITC-R-BLA-00004987." Roche's Response to Request for Admission No. 19. |
| a DNA sequence encoding human erythropoietin | **"genetic instructions for human erythropoietin"** | **Roche's DN2-3α3 cells contain an exogenous DNA sequence encoding human erythropoietin.**<br>"The Epoetin beta (EPO) coding sequence was introduced into CHO cells deficient in the enzyme dihydrofolate reductase (DHFR) by transformation with a linked mouse DHFR, and selection for the DHFR phenotype." ITC-R-BLA-00004934.<br>"High level expression of EPO was achieved by transformation of the DHFR-CHO cells with a vector expressing both EPO and DHFR cDNAs, and subsequent gene amplification by selection in increasing levels of the DHFR inhibitor methotrexate (MTX, and inhibitor of DHFR)." ITC-R-BLA-00004723.<br>"The expression vector for EPO was chosen considering that it should be able to express the cDNA in a CHO cell." ITC-R-BLA-00004723.<br>"As a basis for its denial, Roche directs Amgen to the |

| U.S. PATENT NO. 5,547,933 CLAIM 3 | | |
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| **Claim Limitations** | **Proposed Claim Construction** | **Corresponding Structure or Function in Roche's Product** |
| | | MIRCERA™ BLA, in which Roche admits that "[t]he EPO coding sequence was introduced into CHO cells deficient in the enzyme DHFR by transformation with a linked mouse DHFR cDNA, and selection for the DHFR' phenotype." ITC-R-BLA-00004723." Roche's Response to Request for Admission No. 18.<br><br>"As a basis for its denial, Roche directs Amgen to the MIRCERA™ BLA, in which Roche admits that "[t]he Epoetin beta (EPO) coding sequence was introduced into CHO cells deficient in the enzyme dihydrofolate reductase (DHFR) by transformation with a linked mouse DHFR cDNA and selection for the $DHFR^+$ phenotype. Upon further selection with increasing levels of the drug methotrexate (MTX, an inhibitor of DHFR), the co-integrated DHFR and EPO sequences were amplified to high copy number." ITC-R-BLA-00004987." Roche's Response to Request for Admission No. 19.<br><br>See also ITC-R-BLA-00004722-4727. |
| said product possessing the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells. | **"[said product] causing bone marrow cells to increase production of reticulocytes and red blood cells in the body"** | **The glycoprotein product in RO0503821possesses the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells.**<br>*See '868 claim 1 above.* |

| U.S. PATENT NO. 5,547,933 CLAIM 7 | | |
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| **Claim Limitations** | **Proposed Claim Construction** | **Corresponding Structure or Function in Roche's Product** |
| The glycoprotein product according to claim 3, 4, 5, or 6 | | *See '933 claim 3 above.* |
| wherein the host cell is a non-human mammalian cell. | | *See '868 claim 1 above (CHO cells, mammalian cells).* |

| U.S. PATENT NO. 5,547,933 CLAIM 8 | | |
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| **Claim Limitations** | **Proposed Claim Construction** | **Corresponding Structure or Function in Roche's Product** |
| The glycoprotein product according to claim 7 | | *See '933 claim 7 above.* |
| wherein the non-human mammalian cell is a CHO cell. | | *See '868 claim 1 above (CHO cells, mammalian cells).* |

| U.S. PATENT NO. 5,547,933 CLAIM 9 | | |
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| **Claim Limitations** | **Proposed Claim Construction** | **Corresponding Structure or Function in Roche's Product** |
| A pharmaceutical composition | **"A composition suitable for administration to humans as a pharmaceutical"** | **Roche makes a pharmaceutical composition called MIRCERA (also known as Ro0503821 drug product).** |

| U.S. PATENT NO. 5,547,933 CLAIM 9 | | |
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| **Claim Limitations** | **Proposed Claim Construction** | **Corresponding Structure or Function in Roche's Product** |
| | | "MIRCERA is taken either as an injection into the skin or intravenously." ITC-R-BLA-00000066 (draft package insert).<br><br>"MIRCERA is formulated as a sterile, preservative-free protein solution for intravenous (IV) or subcutaneous (SC) administration." ITC-R-BLA-00000212.<br><br>"RO0503821 is formulated as a sterile, single-use injectable solution contained either in glass vials or in pre-filled syringes (PFS)." ITC-R-BLA-00000309.<br><br>"Injectable solutions of MICERA in vials and prefilled syringes are formulated in an aqueous solution containing sodium phosphate, sodium sulphate, mannitol, methione and poloxamer 188." ITC-R-BLA-00000212.<br><br>*See also* Application Summary for MIRCERA, ITC-R-BLA00000194-691; Information for Patients and Caregivers, ITC-R-BLA-00000066-77.<br>**MIRCERA contains a single drug substance, called RO0503821.**<br><br>"Proprietary name: MIRCERA" "Code designations: RO0503821 (drug substance), Ro 050-3821 (drug product)" ITC-R-BLA-00000248. |
| comprising | | |
| an effective amount of a glycoprotein product effective for | **"a quantity of a glycoprotein product according to claim 1, 2, 3, 4, 5 or 6 that produces a result that in and of itself helps** | **MIRCERA contains an effective amount of the glycoprotein product according to claims 3, 4, and 5 effective for erythropoietin therapy.** |

| U.S. PATENT NO. 5,547,933 CLAIM 9 | | |
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| **Claim Limitations** | **Proposed Claim Construction** | **Corresponding Structure or Function in Roche's Product** |
| erythropoietin therapy according to claim 1, 2, 3, 4, 5 or 6 and | **to heal or cure a patient in the class of patients listed in the specification, column 33 lines 31 through 36: patients generally requiring blood transfusions and including trauma victims, surgical patients, renal disease patients including dialysis patients, and patients with a variety of blood composition affecting disorders, such as hemophilia, sickle cell disease, physiologic anemias, and the like."** | "MIRCERA is a product that acts like the natural hormone – human erythropoietin, which is produced mainly by healthy kidneys. Erythropoietin ensures that enough red blood cells are produced by the body to satisfy oxygen supply to all tissues. MIRCERA is taken either as an injection into the skin or intravenously. . . . MIRCERA is used to treat anemia in patients with chronic kidney disease who may or may not be on dialysis. . . . When you are taking MIRCERA, your healthcare provider will check the effect of the medicine with regular blood tests. Your blood tests may be referred to as 'hemoglobin' and/or 'hematocrit' by your healthcare provider. If these tests show an increase in the number of red blood cells, then MIRCERA is working." ITC-R-BLA-00000066.<br><br>"The efficacy and safety of MIRCERA have been assessed in six phase III randomized multi-center clinical studies for the treatment of anemia in adult patients associated with chronic kidney disease (CKD) including patients on dialysis and not on dialysis." ITC-R-BLA-00000214.<br><br>"The efficacy and safety of RO0503821 was comparable to that of reference treatments (epoetin alfa, epoetin beta, darbepoetin alfa) and resulted in effective anemia management in CKD patients. The 1x2 weeks regimen resulted in similar correction of anemia to the comparator treatment with a high response rate of >90%. Correction of anemia was associated with clinically meaningful improvements in quality of life, supporting the benefit and good tolerability of RO0503821 1x2 weeks treatment for patients in the correction setting." ITC-R-BLA-00000350.<br><br>"Correction of anemia was associated with clinically |

| U.S. PATENT NO. 5,547,933 CLAIM 9 | | |
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| **Claim Limitations** | **Proposed Claim Construction** | **Corresponding Structure or Function in Roche's Product** |
| | | meaningful improvements in quality of life scores as assessed by the SR-36 health questionnaire in both studies." ITC-R-BLA-00000337.<br><br>"RO0503821 was efficacious in correcting anemia associated with CKD in patients who were on dialysis and who were not currently treated with an ESA, regardless of the route of administration (IV or SC). RO0503821 was comparable to both epoetin and darbepoetin alfa reference groups in all study parameters tested with the exception of time to target Hb response in the correction studies, which was longer with RO0503821." ITC-R-BLA-00000326-27.<br><br>*See also* Application Summary for MIRCERA, ITC-R-BLA-00000194-691. |
| a pharmaceutically acceptable diluent, adjuvant or carrier. | **"a diluent, adjuvant, or carrier that is suitable for administration to humans"** | **Roche's MIRCERA pharmaceutical composition contains a pharmaceutically acceptable diluent, adjuvant or carrier.**<br><br>"Injectable solutions of MICERA in vials and prefilled syringes are formulated in an aqueous solution containing sodium phosphate, sodium sulphate, mannitol, methione and poloxamer 188." ITC-R-BLA-00000212.<br><br>"Dosage diluent: 0.01M Sodium phosphate, 0.04 M Sodium sulphate, 0.01 M L-methionine, 3% Mannitol, and 0.01% poloxamer 188 pH 6.2." ITC-R-00025464.<br><br>"RO0503821 is formulated as a sterile, single-use injectable solution contained either in glass vials or in pre-filled syringes (PFS). The aqueous solution for both presentations is the same with regard to the following inactive ingredients: sodium dihydrogen phosphate, sodium sulfate, mannitol, L-methionine, and poloxamer |

| U.S. PATENT NO. 5,547,933 CLAIM 9 | | |
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| **Claim Limitations** | **Proposed Claim Construction** | **Corresponding Structure or Function in Roche's Product** |
| | | 188. The solution does not contain a microbial preservative. This composition for the aqueous solution was used in part of the Phase II program and in all Phase III clinical trials and is the same as that which will be used for future marketing." ITC-R-BLA-00045341.<br><br>"Roche directs Amgen to the MIRCERA™ BLA, in which Roche admits that, for example, one 50 pg/mL vial of the drug product contains an actual weight of 0.06 mg R00503821, 1.788 mg L-Methionine, 6.816 mg Sodium sulphate anhydrous, 1.656 mg Sodium dihydrogen phosphate monohydrate, 36.0 mg Mannitol, 0.12 mg Poloxamer 188, Hydrochloric acid, diluted, q.s. (pH 6.2), Sodium hydroxide solution, q.s. (pH 6.2), Water for Injections q.s. ad total weight. ITC-R-BLA-00003366." Roche's Response to Request for Admission No. 22.<br><br>*See also* ITC-R-IND-00000981; ITC-R-000025758; ITC-R-IND-00002635; Application Summary for MIRCERA, ITC-R-BLA-00000194-691. |

| U.S. PATENT NO. 5,547,933 CLAIM 11 | | |
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| **Claim Limitations** | **Proposed Claim Construction** | **Corresponding Step in Method of Treatment** |
| A method for treating a kidney dialysis patient | | **Roche's agents have performed this method or Roche has induced or will induce physicians to practice the claimed method for treating kidney dialysis patients.** |
| which comprises | | |

| U.S. PATENT NO. 5,547,933 CLAIM 11 | | |
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| **Claim Limitations** | **Proposed Claim Construction** | **Corresponding Step in Method of Treatment** |
| administering a pharmaceutical composition of claim 9 in an amount effective to increase the hematocrit level of said patient. | **"administering a pharmaceutical composition of claim 9 in an amount effective to increase the hematocrit level of said patient"** | **Roche's MIRCERA is administered and will continue to be administered in an amount effective to increase the hematocrit level of patients.**<br><br>"MIRCERA is a product that acts like the natural hormone – human erythropoietin, which is produced mainly by healthy kidneys. Erythropoietin ensures that enough red blood cells are produced by the body to satisfy oxygen supply to all tissues. MIRCERA is taken either as an injection into the skin or intravenously. . . . MIRCERA is used to treat anemia in patients with chronic kidney disease who may or may not be on dialysis. . . . When you are taking MIRCERA, your healthcare provider will check the effect of the medicine with regular blood tests. Your blood tests may be referred to as 'hemoglobin' and/or 'hematocrit' by your healthcare provider. If these tests show an increase in the number of red blood cells, then MIRCERA is working." ITC-R-BLA-00000066.<br><br>"The efficacy and safety of MIRCERA have been assessed in six phase III randomized multi-center clinical studies for the treatment of anemia in adult patients associated with chronic kidney disease (CKD) including patients on dialysis and not on dialysis." ITC-R-BLA-00000214.<br><br>"The efficacy and safety of RO0503821 was comparable to that of reference treatments (epoetin alfa, epoetin beta, darbepoetin alfa) and resulted in effective anemia management in CKD patients. The 1x2 weeks regimen resulted in similar correction of anemia to the comparator treatment with a high response rate of >90%. Correction of anemia was associated with clinically meaningful improvements in quality of life, supporting the benefit and good tolerability of RO0503821 1x2 weeks treatment for |

| U.S. PATENT NO. 5,547,933 CLAIM 11 | | |
|---|---|---|
| **Claim Limitations** | **Proposed Claim Construction** | **Corresponding Step in Method of Treatment** |
| | | patients in the correction setting." ITC-R-BLA-00000350.<br><br>"Correction of anemia was associated with clinically meaningful improvements in quality of life scores as assessed by the SF-36 health questionnaire in both studies." ITC-R-BLA-00000337.<br><br>"RO0503821 was efficacious in correcting anemia associated with CKD in patients who were on dialysis and who were not currently treated with an ESA, regardless of the route of administration (IV or SC). RO0503821 was comparable to both epoetin and darbepoetin alfa reference groups in all study parameters tested with the exception of time to target Hb response in the correction studies, which was longer with RO0503821." ITC-R-BLA-00000326-327.<br><br>"Following a single dose of MIRCERA in CKD patients, the onset of Hb increase (defined as an increase > 0.4 g/dL from baseline) is observed after 7 to 15 days . . . ." ITC-R-BLA-00000213.<br><br>"The conjugates . . . of this invention can be administered in a therapeutically effective amount to patients in the same way EPO is administered." U.S. Patent No. 6,583,272; Col. 3: 23-25.<br><br>*See also* Application Summary for MIRCERA, ITC-R-BLA-00000194-691; Information for Patients and Caregivers, ITC-R-BLA-00000066-77. |

| U.S. PATENT NO. 5,547,933 CLAIM 12 | | |
|---|---|---|
| **Claim Limitations** | **Proposed Claim Construction** | **Corresponding Structure or Function in Roche's Product** |
| A pharmaceutical composition | **"A composition suitable for administration to humans as a pharmaceutical"** | *See '933 claim 9 above.* |
| Comprising | | |
| an effective amount of glycoprotein product effective for erythropoietin therapy according to claim 7 | **"a quantity of a glycoprotein product according to claim 7 that produces a result that in and of itself helps to heal or cure a patient in the class of patients listed in the specification, column 33 lines 31 through 36: patients generally requiring blood transfusions and including trauma victims, surgical patients, renal disease patients including dialysis patients, and patients with a variety of blood composition affecting disorders, such as hemophilia, sickle cell disease, physiologic anemias, and the like."** | *See '933 claim 9 above (effective amount of glycoprotein product effective for erythropoietin therapy).*<br><br>*See '933 claim 7 above.* |
| and a pharmaceutically acceptable diluent, adjuvant or carrier. | | **Roche's MIRCERA pharmaceutical composition contains a pharmaceutically acceptable diluent, adjuvant or carrier.**<br><br>*See '933 claim 9 above.* |

| U.S. PATENT NO. 5,547,933 CLAIM 14 | | |
|---|---|---|
| **Claim Limitations** | **Proposed Claim Construction** | **Corresponding Structure or Function in Roche's Product** |
| A method for treating a kidney dialysis patient | | **Roche's agents have performed this method or Roche has induced or will induce physicians to practice the claimed method for treating kidney dialysis patients.**<br><br>*See '933 claim 11 above.* |
| which comprises | | |
| administering a pharmaceutical composition of claim 12 in an amount effective to increase the hematocrit level of said product. | **"administering a pharmaceutical composition of claim 12 in an amount effective to increase the hematocrit level of said patient"**<br><br>(Note: the limitation contains a typographical error, the term "product" should read "patient" as in '933 claim 11). | **Roche's MIRCERA is administered and will continue to be administered in an amount effective to increase the hematocrit level of patients.**<br><br>*See '933 claims 11 and 12 above.* |

| U.S. PATENT NO. 5,955,422 CLAIM 1 | | |
|---|---|---|
| **Claim Limitations** | **Proposed Claim Construction** | **Corresponding Structure or Function in Roche's Product** |
| A pharmaceutical composition | **"A composition suitable for administration to humans"** | **Roche's MIRCERA product is a pharmaceutical composition.**<br><br>*See '933 claim 9 above (pharmaceutical composition).* |
| comprising | **"containing at least"** | |

| U.S. PATENT NO. 5,955,422 CLAIM 1 | | |
|---|---|---|
| **Claim Limitations** | **Proposed Claim Construction** | **Corresponding Structure or Function in Roche's Product** |
| a therapeutically effective amount of human erythropoietin | **"therapeutically effective" means either:**[3]<br><br>**(a) "therapeutically effective amount is one that elicits any one or all of the effects often associated with in vivo biological activity of natural EPO, such as those listed in the specification, column 33, lines 16 through 22: stimulation of reticulocyte response, development of ferrokinetic effects (such as plasma iron turnover effects and marrow transit time effects), erythrocyte mass changes, stimulation of hemoglobin C synthesis and, as indicated in Example 10, increasing hematocrit levels in mammals."**<br><br>**or**<br><br>**(b) "a quantity that produces a result that in and of itself helps to heal or cure. A therapeutically effective amount is one that shares the in vitro biological activity of natural EPO, elicits in vivo biological effects such as those listed in the specification, column 33, lines 24-28: stimulation of reticulocyte response, development of ferrokinetic effects(such as plasma iron turnover effects and marrow transit time effects), erythrocyte mass changes, stimulation of hemoglobin C synthesis, and, as indicated in Example 10, increases the** | **Roche's MIRCERA product contains a therapeutically effective amount of human erythropoietin under both claim construction (a) and claim construction (b).**<br>*See '933 claim 9 above.*<br><br>**Roche's MIRCERA contains human erythropoietin.**<br><br>*See '868 claim 1 above.* |

[3] Construction (a) reflects the claim construction adopted by the Federal Circuit in *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 457 F.3d 1293, 1303 (Fed. Cir. 2006). Amgen, however, has not yet exhausted it right to appeal that construction. Amgen, therefore, reserves the right to propose claim construction (b) at trial.

| U.S. PATENT NO. 5,441,868 CLAIM 1 | | |
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| **Claim Limitations** | **Proposed Claim Construction** | **Corresponding Step in Roche's Production Process** |
| | | material. Epoetin beta, a recombinant erythropoietin, is manufactured at Roche Pharma Biotechnology Production in Penzberg, Germany.<br>The EPO starting material remained unchanged during the process development of RO0503821." ITC-R-BLA-00004178.<br><br>"Epoetin beta is a synthetic glycoprotein produced by recombinant DNA technology in Chinese hamster ovarian (CHO) cells." ITC-R-IND-000000979.<br><br>"[I]t was demonstrated by means of extended characterization using different analytical methods that apart from slight quantitative differences, the carbohydrate structure of RO0503821 remains unchanged as compared to EPO starting material." ITC-R-BLA-00004317.<br><br>"Figure 14 compares the relative contents of the different structures found in Ro 50-3821 and unmodified EPO. All oligosaccharide structures known from unmodified recombinant EPO are also present in Ro 50-3821. The chromatogram provides no evidence for altered oligosaccharide structures after pegylation of EPO (see Figure 13)." Comparability Program for Ro 50-3821 Drug Substance 5/21/03, p. 1-69 ITC-R-00090941, at 91008<br><br>"Figure 9 compares the relative contents of the different structures found in pegylated EPO and unmodified EPO. All oligosaccharide structures knowen from unmodified EPO are also present in Ro 50-3821. The chromatogram provides no evidence for altered oligosaccharide structures after pegylation of EPO (see figure 8). From a quantitative point of view small differences could be seen in the oligosaccharide pattern between pegylated EPO and |

| U.S. PATENT NO. 5,441,868 CLAIM 1 | | |
|---|---|---|
| **Claim Limitations** | **Proposed Claim Construction** | **Corresponding Step in Roche's Production Process** |
| | | unmodified EPO (see figure 9)." ITC-R-IND-00005504-5531, at 5521.<br><br>"Ro 50-3821 is a synthetic human erythropoietin, epoetin beta, produced by recombinant DNA technology which is then modified by chemically conjugating one linear methoxy-polyethylene glycol molecule to its N-terminus or lysine residue." ITC-R-IND-00000542.<br><br>"RO0503821 is comprised of human epoetin beta (EPO, Ro 205-3859), which is mono-peglated with a linear methoxy-polyethlene glcol (PEG), with an average molecular weight of around 30 kDa. RO0503821 is the reaction product of EPO and methoxy-polyethlene glycol-succinimidyl butyric acid (Ro 50-3919). The only difference in the composition of native and modified protein is due to the formation of an amide bond between the amino group of EPO and the PEG molecule at the point of attachment." ITC-R-00076642<br><br>"PEG-EPO (Ro 50-3821) is comprised of human epoetin beta (Ro 205-3859), which is mono-pegylated with a linear methoxy-polyethylene glycol (PEG) with an average molecular weight of 32 kDa. PEG-EPO consists of at least 90% mono-pegylated EPO and the remainder is comprised of di-pegylated EPO, higher pegylated EPO and non-pegylated EPO (less than 1%)." ITC-R-00050625<br><br>"The experimental drug used in this study, Ro 50-3821 is a new compound, which is similar to the human hormone erythropoietin. Like currently available drugs called epoetins, Ro 50-3821 can increase the number of red blood cells and hemoglobin levels in the blood. Ro 50-3821 is also produced by genetic engineering techniques, but the |

| U.S. PATENT NO. 5,441,868 CLAIM 1 | | |
|---|---|---|
| **Claim Limitations** | **Proposed Claim Construction** | **Corresponding Step in Roche's Production Process** |
| | | drug is manufactured in such a way that to the drug [sic] can stay in the body's circulation for a long time." ITC-R-IND-00000771.<br><br>"The Defendants' EPO [Recormon] is a glycoprotein the polypeptide element of which has the amino acid sequence set out in Schedule 1 hereto." [Schedule 1 is Fig. 6 1-165] DEFENDANTS' ADMISSIONS at ¶2, 2/7/95, *Kirin-Amgen v. Boehringer Mannheim.*<br><br>"Ro 50-3821/000 (PEG/EPO) is comprised of erythropoietin (EPO) with a linear methoxy-PEG molecule attached to it." ITC-R-BLA-00008462.<br><br>"PEG-EPO (Ro 50-3821) is a pegylated version of Epoetin beta, whereby one linear polyethylene glycol chain has been added to the recombinant erythropoietin molecule." ITC-R-IND-00070631.<br><br>*See also* ITC-R-BLA-00006908; ITC-R-BLA-00013120 at 00013131; Farid Depo. Tr. 184:22-185:7, ITC-R-00076640; ITC-R-BLA-00019133 at 19136; ITC-R-BLA-00000005 at 00006287; ITC-R-BLA-00018966 at 18969; ITC-R-BLA-00016194 at 00016202; ITC-R-BLA-00016096 at 00016104; ITC-R-IND-00062646; ITC-R-IND-00000542; ITC-R-BLA-00007319 at 00007349; ITC-R-BLA-00002509 at 00002525; ITC-R-00076642; ITC-R-BLA-00004027; ITC-R-IND-00000542; ITC-R-IND-00000979; Application Summary for MIRCERA, ITC-R-BLA-00000194-691; Drug Substance – RO0503821, ITC-R-BLA-00004024-4650.<br><br>**Roche has referred to RO0503821 (and its formulated drug product) by a variety of terms, indicating that it** |

| U.S. PATENT NO. 5,441,868 CLAIM 1 | | |
|---|---|---|
| **Claim Limitations** | **Proposed Claim Construction** | **Corresponding Step in Roche's Production Process** |
| | | **comprises a glycosylated erythropoeitin polypeptide.**<br><br>"pegylated erythropoietin": ITC-R-00074400; ITC-R-BLA-00007110; ITC-R-BLA-00007088.<br><br>"pegylated EPO": ITC-R-BLA-00013133; ITC-R-00074354; ITC-R-BLA-0007087; ITC-R-BLA-00010167.<br><br>"pegylated epoetin beta": ITC-R-BLA-00007084; ITC-R-BLA-00007107; ITC-R-BLA-00010161.<br><br>"pegylated epoetin": ITC-R-00001783, ITC-R-00045054-055.<br><br>"pegylated human epoetin-beta": ITC-R-BLA-00007081; ITC-R-BLA-00007104.<br><br>"a pegylated version of epoetin beta": ITC-R-BLA-00007087; ITC-R-BLA-00007109; ITC-R-BLA-00007349.<br><br>"PEG-EPOETIN": ITC-R-00001782<br><br>"a pegylated form of erythropoietin": ITC-R-BLA-00016106.<br><br>"PEGylated recombinant human erythropoietin": ITC-R-BLA-00018452.<br><br>"mono-pegylated EPO": ITC-R-00050494.<br><br>"PEG-EPO": ITC-R-BLA-00019133; ITC-R-BLA-00006908; ITC-R-BLA-00007319; ITC-R-BLA-00007375; ITC-R-IND-00070631. |

| U.S. PATENT NO. 5,441,868 CLAIM 1 | | |
|---|---|---|
| **Claim Limitations** | **Proposed Claim Construction** | **Corresponding Step in Roche's Production Process** |
| | | "polyethylene glycol conjugated recombinant human epoetin beta": ITC-R-BLA-00006925; ITC-R-BLA-00007324; ITC-R-BLA-00010188; ITC-R-BLA-00011363; ITC-R-BLA-00014323.<br><br>"a formulation of epoetin beta chemically linked to PEG": ITC-R-BLA-00024728.<br><br>"rhEPO (recombinant human erythropoietin) conjugated with 32KD PEG-SBA": ITC-R-BLA-00016104.<br><br>"methoxy polyethylene glycol-epoetin beta": ITC-R-BLA-00000248; ITC-R-BLA-00000230; ITC-R-IND-00026730.<br><br>"CERA": ITC-R-00024874; ITC-R-00003851; ITC-R-BLA-00018439. |
| having the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells | **"causing bone marrow cells to increase production of reticulocytes and red blood cells in the body"** | **The glycosylated erythropoietin polypeptide in RO0503821 has the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells.**<br><br>"MIRCERA stimulates the bone marrow to make red blood cells." ITC-R-BLA-00000066.<br><br>"RO0503821 stimulates erythropoeisis thereby increasing the number of RBCs." ITC-R-BLA-00000316.<br><br>"RO0503821 is a stimulator of erythroid progenitor cells in the bone marrow. … The activity determination is based on the measurement of the increase in reticulocyte production after parenteral administration of the |

| U.S. PATENT NO. 5,441,868 CLAIM 1 | | |
|---|---|---|
| **Claim Limitations** | **Proposed Claim Construction** | **Corresponding Step in Roche's Production Process** |
| | | RO0503821 to normal healthy mice." ITC-R-BLA-00004030<br><br>"Ro 50-3821 is a mono-pegylated form of epoetin beta, a recombinant human erythropoietin. The pharmacological action of Ro 50-3821 is identical to that of erythropoietin beta in binding to surface receptors of erythroid progenitor cells to trigger proliferation, maturation and terminal differentiation of colony-forming units." ITC-R-IND-00062646<br><br>"The mode of action for RO0503821 is described by the following key mechanism: receptor binding and stimulation of production of erythroid progenitor cells in the bone marrow." ITC-R-BLA-00004200.<br><br>"The pharmacological action of Ro 50-3821 is identical to that of erythropoietin beta in binding to surface receptors of erythroid progenitor cells to trigger proliferation, maturation, and terminal differentiation of colony-forming units." ITC-R-IND-00062646.<br><br>"The pharmacological action of R0 50-3821 is identical to that of epoetin beta in stimulating erythropoeisis by triggering proliferation, maturation and terminal differentiation of the colony-forming unit-erythroids (CFU-E) in the bone marrow through binding to its receptors on the surface of these progenitor cells." ITC-R-IND-00000542.<br><br>"This invention provides conjugates, said conjugates comprising an erythropoietin glycoprotein having at least one free amino group and having the in vivo biological activity of causing bone marrow cells to increase |

| U.S. PATENT NO. 5,441,868 CLAIM 1 | | |
|---|---|---|
| **Claim Limitations** | **Proposed Claim Construction** | **Corresponding Step in Roche's Production Process** |
| | | production of reticulocytes and red blood cells and selected from the group consisting of human erythropoietin...." U.S. Patent No. 6,583,272, Col. 2:56-61.<br><br>"The conjugates in accordance of this invention can be administered in a therapeutically effective amount to patients in the same way EPO is administered. The therapeutically effective amount is that amount of conjugate necessary for the in vivo biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells." U.S. Patent No. 6,583,272, Col. 3:23-29.<br><br>*See also* ITC-R-IND-00070631; Application Summary for MIRCERA, ITC-R-BLA-00000194-384; Information for Patients and Caregivers, ITC-R-BLA-00000066-77. |
| comprising the steps of: | **"containing at least the following steps"** | |
| (a) growing, under suitable nutrient conditions, mammalian host cells | **"growing, under conditions appropriate and conducive to mammalian host cell growth, cells from a warm-blooded animal, whose young are fed by milk secreted from mammary glands"** | **Roche grows mammalian host cells (Chinese Hamster Ovary ("CHO") cells) under suitable (appropriate) nutrient conditions as part of the manufacturing process for RO0503821.**<br><br>"Epoetin beta (EPO) is produced by the recombinant CHO cell line DN2-3α3 in suspension culture." ITC-R-BLA-00004667<br><br>"In order to produce a recombinant EPO with properties similar to the natural EPO, Genetics Institute decided to use a mammalian vector/host expression system. The advantages of the system selected (gene amplification in Chinese hamster ovary (CHO) cells) are that the protein is folded, disulfide linked, glycosylated, and secreted into the |

| U.S. PATENT NO. 5,441,868 CLAIM 1 | | |
|---|---|---|
| **Claim Limitations** | **Proposed Claim Construction** | **Corresponding Step in Roche's Production Process** |
| | | growth medium." ITC-R-BLA-00004803.<br><br>"Compositions of the Media." ITC-R-BLA-00004674-4676.<br><br>"Roche further admits that 'Epoetin beta is a glycoprotein produced by recombinant DNA technology in Chinese hamster ovary cells.'" Roche's Response to Request for Admission No. 12 (quoting ITC-R-BLA-00000230).<br><br>"EPO is produced in suspension culture in an 1,000 L bioreactor scale in a production process without using animal and human derived raw materials." ITC-R-00076656.<br><br>"The said CHO cells are cultured under suitable nutrient conditions in a manner allowing said CHO cells to express the Defendants' EPO." DEFENDANTS' ADMISSIONS at ¶7, 2/7/95, *Kirin-Amgen v. Boehringer Mannheim.*<br><br>"The said CHO cells are eucaryotic, mammalian cells and are capable of glycosylating the polypeptide element of the Defendants' EPO." DEFENDANTS' ADMISSIONS at ¶6, 2/7/95, *Kirin-Amgen v. Boehringer Mannheim.*<br><br>*See also* Drug Substance – RO0503821, ITC-R-BLA-00004024-4650. |
| transformed or transfected with an isolated DNA sequence encoding human erythropoietin; and | **"[said cells] receiving the purified genetic instructions for human erythropoietin; and"** | **The DN2-3α3 cells used by Roche during the manufacturing process for RO0503821 have been transformed or transfected with an isolated DNA sequence encoding human erythropoietin.**<br><br>"The Epoetin beta (EPO) coding sequence was introduced into CHO cells deficient in the enzyme dihydrofolate |

| U.S. PATENT NO. 5,441,868 CLAIM 1 | | |
|---|---|---|
| **Claim Limitations** | **Proposed Claim Construction** | **Corresponding Step in Roche's Production Process** |
| | | reductase (DHFR) by transformation with a linked mouse DHFR, and selection for the DHFR phenotype." ITC-R-BLA-00004934.<br><br>"High level expression of EPO was achieved by transformation of the DHFR-CHO cells with a vector expressing both EPO and DHFR cDNAs, and subsequent gene amplification by selection in increasing levels of the DHFR inhibitor methotrexate (MTX, and inhibitor of DHFR)." ITC-R-BLA-00004723.<br><br>"In order to produce a recombinant EPO with properties similar to the natural EPO, Genetics Institute decided to use a mammalian vector/host expression system. The advantages of the system selected (gene amplification in Chinese hamster ovary (CHO) cells) are that the protein is folded, disulfide linked, glycosylated, and secreted into the growth medium." ITC-R-BLA-00004803.<br><br>"The expression vector for EPO was chosen considering that it should be able to express the cDNA in a CHO cell." ITC-R-BLA-00004723.<br><br>"As a basis for its denial, Roche directs Amgen to the MIRCERA™ BLA, in which Roche admits that '[t]he EPO coding sequence was introduced into CHO cells deficient in the enzyme DHFR by transformation with a linked mouse DHFR cDNA, and selection for the $DHFR^+$ phenotype.' ITC-R-BLA-00004723." Roche's Response to Request for Admission No. 18.<br><br>"As a basis for its denial, Roche directs Amgen to the MIRCERA™ BLA, in which Roche admits that '[t]he Epoetin beta (EPO) coding sequence was introduced into |

| U.S. PATENT NO. 5,441,868 CLAIM 1 | | |
|---|---|---|
| **Claim Limitations** | **Proposed Claim Construction** | **Corresponding Step in Roche's Production Process** |
| | | CHO cells deficient in the enzyme dihydrofolate reductase (DHFR) by transformation with a linked mouse DHFR cDNA and selection for the $DHFR^+$ phenotype. Upon further selection with increasing levels of the drug methotrexate (MTX, an inhibitor of DHFR), the co-integrated DHFR and EPO sequences were amplified to high copy number.' ITC-R-BLA-00004987." Roche's Response to Request for Admission No. 19.<br><br>*See also* Drug Substance – RO0503821, ITC-R-BLA-00004024-4650. |
| (b) isolating said glycosylated erythropoietin polypeptide therefrom. | **"recovering in pure form said glycosylated erythropoietin polypeptide."** | **Roche isolates the glycosylated erythropoietin polypeptide in RO0503821 from the cell culture medium.**<br><br>"During the transfer the harvest is cooled to ≤ 15° C by a heat exchanger. Afterwards the cells are removed by disk stack centrifugation and discarded. The supernatant containing EPO is in-line filtered and collected in a second pre-cooled vessel. . . . After 2 hours of incubation the cell free supernatant is filtered again to remove precipitates. The supernatant is kept ≤ 15° C and loaded onto a Blue Sepharose column within 36 hours. Each harvest is processed separately during purification." ITC-R-BLA-00004673-74.<br><br>"The Epoetin beta purification process consists of five chromatographic steps. This process starts with a capture step using Blue Sepharose (BS) chromatography. Further purification is performed using a hydrophobic interaction chromatography on Butyl Toyopearl (BU), an adsorption chromatography on Hydroxyapatite Ultrogel (HA), a reversed phase (RP-) preparative HPLC on Vydac $C_4$ and finally an anion exchange chromatography on DEAE |

| U.S. PATENT NO. 5,441,868 CLAIM 1 | | |
|---|---|---|
| **Claim Limitations** | **Proposed Claim Construction** | **Corresponding Step in Roche's Production Process** |
| | | Sepharose (DEAE)" ITC-R-BLA-00004682.<br><br>"Each harvest undergoes purification which leads to 10 batches of purified EPO starting material." ITC-R-BLA-00004667<br><br>*See also* ITC-R-BLA-00004673-4681; Drug Substance – RO0503821, ITC-R-BLA-00004024-4650. |

| U.S. PATENT NO. 5,441,868 CLAIM 2 | | |
|---|---|---|
| **Claim Limitations** | **Proposed Claim Construction** | **Corresponding Step in Roche's Production Process** |
| The process according to claim 1 | | *See '868 claim 1 above.* |
| wherein said host cells are CHO cells. | | **Roche uses CHO cells to produce the glycosylated erythropoietin polypeptide in RO0503821.**<br>*See '868 claim 1 above.* |

| U.S. PATENT NO. 5,618,698 CLAIM 4 | | |
|---|---|---|
| **Claim Limitations** | **Proposed Claim Construction** | **Corresponding Step in Roche's Production Process** |
| A process for the production of a glycosylated erythropoietin polypeptide | **"A process for the production of an erythropoietin polypeptide having one or more carbohydrate groups attached to the polypeptide"** | **Roche uses the recited process to produce the glycosylated erythropoietin polypeptide in RO0503821.**<br>*See '868 claim 1 above.* |

| U.S. PATENT NO. 5,618,698 CLAIM 4 | | |
|---|---|---|
| **Claim Limitations** | **Proposed Claim Construction** | **Corresponding Step in Roche's Production Process** |
| having the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells | **"causing bone marrow cells to increase production of reticulocytes and red blood cells in the body"** | **The glycosylated erythropoietin polypeptide in RO0503821 has the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells.**<br>*See '868 claim 1 above.* |
| comprising the steps of: | **"containing at least the following steps"** | |
| a) growing, under suitable nutrient conditions, vertebrate cells comprising | **"growing, under conditions appropriate and conducive to vertebrate cell growth, cells originating from an animal having a segmented body or cartilaginous spinal cord, containing at least"** | **Roche grows vertebrate host cells (DN2-3α3 cells) under suitable (appropriate) nutrient conditions as part of the manufacturing process for RO0503821.**<br>"Epoetin beta (EPO) is produced by the recombinant CHO cell line DN2-3α3 in suspension culture." ITC-R-BLA-00004667<br>"In order to produce a recombinant EPO with properties similar to the natural EPO, Genetics Institute decided to use a mammalian vector/host expression system. The advantages of the system selected (gene amplification in Chinese hamster ovary (CHO) cells) are that the protein is folded, disulfide linked, glycosylated, and secreted into the growth medium." ITC-R-BLA-00004803.<br>"Compositions of the Media." ITC-R-BLA-00004674-4676.<br>"Roche further admits that 'Epoetin beta is a glycoprotein produced by recombinant DNA technology in Chinese hamster ovary cells.'" Roche's Response to Request for Admission No. 12 (quoting ITC-R-BLA-00000230). |

| U.S. PATENT NO. 5,618,698 CLAIM 4 | | |
|---|---|---|
| **Claim Limitations** | **Proposed Claim Construction** | **Corresponding Step in Roche's Production Process** |
| | | "EPO is produced in suspension culture in an 1,000 L bioreactor scale in a production process without using animal and human derived raw materials." ITC-R-00076656.<br><br>"The said CHO cells are cultured under suitable nutrient conditions in a manner allowing said CHO cells to express the Defendants' EPO." DEFENDANTS' ADMISSIONS at ¶7, 2/7/95, *Kirin-Amgen v. Boehringer Mannheim.*<br><br>"The said CHO cells are eucaryotic, mammalian cells and are capable of glycosylating the polypeptide element of the Defendants' EPO." DEFENDANTS' ADMISSIONS at ¶6, 2/7/95, *Kirin-Amgen v. Boehringer Mannheim.*<br><br>*See also* ITC-R-BLA-00004722-4727; Drug Substance – RO0503821, ITC-R-BLA-00004024-4650. |
| promoter DNA, other than human erythropoietin promoter DNA, | **"DNA sequences that initiate transcription of a gene, which DNA is not a human genomic EPO promoter DNA."** | **DN2-3α3 cells contain promoter DNA (the adenovirus type 2 major late promoter), other than human erythropoietin promoter DNA.**<br><br>"The vector contains four known promoters that could be functional in mammalian cells. The expression of the inserted [EPO] cDNA is driven by the adenovirus type 2 major late promoter found in fragment 6." ITC-R-BLA-00004804.<br><br>"Roche directs Amgen to the MIRCERA™ BLA, in which Roche admits that '[t]he [expression] vector contains four known promoters that could be functional in mammalian cells. . . . It is possible that some of the EPO mRNA in the expressing DN2-3α3 line is derived from transcription initiating at the SV40 early promoter in fragment 5.' ITC-R-BLA- |

| U.S. PATENT NO. 5,618,698 CLAIM 4 | | |
|---|---|---|
| **Claim Limitations** | **Proposed Claim Construction** | **Corresponding Step in Roche's Production Process** |
| | | 00004804." Roche's Response to Request for Admission No. 20.<br>*See also* ITC-R-BLA-00004722-4727. |
| operatively linked to | **"[the promoter DNA] is linked to the EPO DNA in a way that maintains the capability of the promoter DNA to initiate transcription of the EPO DNA."** | **The adenovirus type 2 major late promoter DNA of the DN2-3α3 cells is linked to the EPO DNA in a way that maintains the ability of the adenovirus type 2 major late promoter to initiate transcription of the EPO DNA.**<br>"The vector contains four known promoters that could be functional in mammalian cells. The expression of the inserted [EPO] cDNA is driven by the adenovirus type 2 major late promoter found in fragment 6." ITC-R-BLA-00004804.<br>*See also* ITC-R-BLA-00004722-4727. |
| DNA encoding the mature erythropoietin amino acid sequence of FIG. 6; and | **"the genetic instructions for the 166 amino acid residues (+1 through +166) specified in Fig. 6"** | **DN2-3α3 cells contain the DNA sequence encoding the entire 166 amino acid sequence (+1 through +166) depicted in Figure 6 of the '698 patent, including DNA encoding an arginine at position 166.**<br>"Epoetin beta (EPO) cDNA codes for a 166 amino acid polypeptide. All EPO products analyzed so far – either from human urine or recombinant production – only contain 165 amino acids, missing the last arginine residue." ITC-R-BLA-00005616.<br>Figure 2 from ITC-R-BLA-00004735-4738(structure of cDNA showing 166aa).<br>*See also* ITC-R-BLA-00004728-4740. |
| b) isolating said glycosylated erythropoietin | **"recovering in pure form said glycosylated erythropoietin polypeptide expressed by said cells"** | **The glycosylated erythropoietin polypeptide in RO0503821 is isolated after expression from the DN2-3α3 cells.** |

| U.S. PATENT NO. 5,618,698 CLAIM 4 | | |
|---|---|---|
| **Claim Limitations** | **Proposed Claim Construction** | **Corresponding Step in Roche's Production Process** |
| polypeptide expressed by said cells. | | *See '868 claim 1 above.* |

| U.S. PATENT NO. 5,618,698 CLAIM 5 | | |
|---|---|---|
| **Claim Limitations** | **Proposed Claim Construction** | **Corresponding Step in Roche's Production Process** |
| The process of claim 4 | | *See '698 claim 4 above* |
| wherein said promoter DNA is viral promoter DNA. | **"The process of claim 4 where the promoter DNA originates from a virus"** | **Roche's DN2-3α3 cells contain viral promoter DNA (the adenovirus type 2 major late promoter).**<br>*See '698 claim 4 above.* |

| U.S. PATENT NO. 5,618,698 CLAIM 6 | | |
|---|---|---|
| **Claim Limitations** | **Proposed Claim Construction** | **Corresponding Step in Roche's Production Process** |
| A process for the production of a glycosylated erythropoietin polypeptide | *See '698 claim 4 above.* | **Roche uses the recited process to produce the glycosylated erythropoietin polypeptide in RO0503821.**<br>*See '868 claim 1 above.* |
| having the in vivo biological property of causing bone marrow cells to increase production of | *See '698 claim 4 above.* | **The glycosylated erythropoietin polypeptide in RO0503821 has the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells.** |

| U.S. PATENT NO. 5,618,698 CLAIM 6 | | |
|---|---|---|
| **Claim Limitations** | **Proposed Claim Construction** | **Corresponding Step in Roche's Production Process** |
| reticulocytes and red blood cells | | *See '868 claim 1 above.* |
| comprising the steps of: | | |
| a) growing, under suitable nutrient conditions, vertebrate cells comprising | *See '698 claim 4 above.* | **Roche grows vertebrate host cells (DN2-3α3 cells) under suitable (appropriate) nutrient conditions as part of the manufacturing process for RO0503821.**<br>*See '698 claim 4 above.* |
| amplified DNA encoding the mature erythropoietin amino acid sequence of FIG. 6; and | **"amplified" means "an increased number of copies relative to other DNA sequences in the genome"**<br><br>**"DNA encoding the mature erythropoietin amino acid sequence of FIG. 6," *see '698 claim 4 above.*** | **Roche's DN2-3α3 cells contain amplified DNA encoding the mature erythropoietin amino acid sequence of Figure 6 in the '698 Patent.**<br><br>**The DNA encodes the mature erythropoietin amino acid sequence of Figure 6.**<br><br>*See '698 claim 4 above.*<br><br>**The DNA encoding the mature erythropoietin amino acid sequence of Figure 6 is amplified.**<br><br>"The Epoetin beta (EPO) coding sequence was introduced into CHO cells deficient in the enzyme dihydrofolate reductase (DHFR) by transformation with a linked mouse DHFR cDNA, and selection for $DHFR^+$ phenotype. Upon further selection with increasing levels of the drug methotrexate (MTX, an inhibitor of (DHFR), the co-integrated DHFR and EPO sequences were amplified to high copy number." ITC-R-BLA-00004987<br><br>"High level expression of EPO was achieved by |

| U.S. PATENT NO. 5,618,698 CLAIM 6 | | |
|---|---|---|
| **Claim Limitations** | **Proposed Claim Construction** | **Corresponding Step in Roche's Production Process** |
| | | transformation of the DHFR-CHO cells with a vector expressing both EPO and DHFR cDNAs, and subsequent gene amplification by selection in increasing levels of the DHFR inhibitor methotrexate (MTX, and inhibitor of DHFR)." ITC-R-BLA-00004723.<br><br>"In order to produce a recombinant EPO with properties similar to the natural EPO, Genetics Institute decided to use a mammalian vector/host expression system. The advantages of the system selected (gene amplification in Chinese hamster ovary (CHO) cells) are that the protein is folded, disulfide linked, glycosylated, and secreted into the growth medium." ITC-R-BLA-00004803.<br><br>"The expression vector for Epoetin beta (EPO) was chosen considering that it should be able to express the cDNA in a Chinese hamster ovary (CHO) cell. The vector also contains a drug resistance marker, sequential application of increasing levels of the drug allows selecting progeny cell lines that have amplified the drug resistance gene, co-amplified the EPO gene, and produce high levels of the recombinant protein." ITC-R-BLA-00004934 |
| b) isolating said glycosylated erythropoietin polypeptide expressed by said cells. | *See '698 claim 4 above.* | **The glycosylated erythropoietin polypeptide in RO0503821 is isolated after expression from the DN2-3α3 cells.**<br><br>*See '868 claim 1 above.* |

| U.S. PATENT NO. 5,618,698 CLAIM 7 | | |
|---|---|---|
| **Claim Limitations** | **Proposed Claim Construction** | **Corresponding Step in Roche's Production Process** |
| The process of claim 6 | | *See '868 claim 6 above* |
| wherein said vertebrate cells further comprise amplified marker gene DNA. | **"The process of claim 6 where the vertebrate cells also include a gene which codes for a substance used to identify or select cells having a desirable characteristic."** | **Roche's DN2-3α3 cells contain amplified marker gene DNA -- Dihydrofolate reductase ("DHFR") gene DNA.**<br><br>"The vector also contains a drug resistance marker, sequential application of increasing levels of the drug allows selecting progeny cell lines that have amplified the drug restance gene, co-amplified the EPO gene, and produce high levels of the recombinant protein." ITC-R-BLA-00004934<br><br>"High level expression of EPO was achieved by transformation of the DHFR-CHO cells with a vector expressing both EPO and DHFR cDNAs, and subsequent gene amplification by selection in increasing levels of the DHFR inhibitor methotrexate (MTX, and inhibitor of DHFR)." ITC-R-BLA-00004723.<br><br>"The expression vector DN2-3 containing the EPO cDNA linked to the mouse DHFR gene was inserted into DHFR deficient DUKX-B11 CHO cells by protoplast fusion. Subsequently, selection of the $DHFR^+$ phenotype was performed. Upon further selection in increasing levels of the drug methotrexate (MTX, an inhibitor of DHFR), the co-integrated DHFR and EPO sequences were amplified to high numbers." ITC-R-00076652.<br><br>"The Epoetin beta (EPO) coding sequence was introduced into CHO cells deficient in the enzyme dihydrofolate reductase (DHFR) by transformation with a linked mouse DHFR cDNA, and selection for $DHFR^+$ phenotype. Upon |

| | | |
|---|---|---|
| | | further selection with increasing levels of the drug methotrexate (MTX, an inhibitor of (DHFR), the co-integrated DHFR and EPO sequences were amplified to high copy number." ITC-R-BLA-00004987<br>*See also* ITC-R-BLA-00004722-4727. |

| U.S. PATENT NO. 5,618,698 CLAIM 8 | | |
|---|---|---|
| **Claim Limitations** | **Proposed Claim Construction** | **Corresponding Step in Roche's Production Process** |
| The process of claim 7 | | *See '698 claim 7 above.* |
| wherein said amplified marker gene DNA is Dihydrofolate reductase (DHFR) gene DNA. | **"The process of claim 7 where the amplified marker gene DNA is DHFR, which is a specific enzyme which selects for survival of cells."** | **Roche's DN2-3α3 cells contain amplified Dihydrofolate reductase ("DHFR") gene DNA.**<br>*See '698 claim 7 above.* |

| U.S. PATENT NO. 5,618,698 CLAIM 9 | | |
|---|---|---|
| **Claim Limitations** | **Proposed Claim Construction** | **Corresponding Step in Roche's Production Process** |
| The process according to claims 2, 4 and 6 | | *See above re '698 claims 4 and 6* |
| wherein said cells are mammalian cells. | **"cells from a warm-blooded animal, whose young are fed by milk secreted from mammary glands"** | **Roche's DN2-3α3 cells are mammalian cells.**<br>*See '868 claim 1 above (CHO cells, mammalian cells).* |

| U.S. PATENT NO. 5,756,349 CLAIM 7 | | |
|---|---|---|
| **Claim Limitations** | **Proposed Claim Construction** | **Corresponding Step in Roche's Production Process** |
| A process for producing erythropoietin | **"a process for producing erythropoietin"** | **Roche uses the recited process to produce the erythropoietin in RO0503821.**<br>*See '868 claim 1.* |
| comprising the step of | **"containing at least the steps of"** | |
| culturing, under suitable nutrient conditions, vertebrate cells according to claim 1, 2, 3, 4, 5 or 6. | **"the act of growing in vitro, under conditions appropriate and conducive to vertebrate cell growth, cells originating from an animal having a segmented body or cartilaginous spinal cord, according to claim 1, 2, 3, 4, 5 or 6"** | **Roche's process for producing the erythropoietin in RO0503821 includes culturing, under suitable nutrient conditions, vertebrate cells (DN2-3α3 cells) according to Claim 1, 2 or 3 of the '349 patent.**<br>*See '698 claim 4 above (growing/culturing CHO cells under suitable nutrient conditions).*<br>*See '349 claim 1 below (independent claim).* |

| U.S. PATENT NO. 5,756,349 CLAIM 1 | | |
|---|---|---|
| **Claim Limitations** | **Proposed Claim Construction** | **Corresponding Structure or Function in Roche's Vertebrate Cells** |
| Vertebrate cells | *See '349 claim 7 above.* | **Roche's DN2-3α3 cells are vertebrate cells.**<br>*See '698 claim 4 above.* |
| which can be propagated in vitro and | **"which can be grown in culture outside of a living body"** | **Roche's DN2-3α3 cells can be propagated in vitro.**<br>"Epoetin beta (EPO) is produced by the recombinant CHO cell line DN2-3α3 in suspension culture." ITC-R-BLA-00004667<br>"In order to produce a recombinant EPO with properties similar to the natural EPO, Genetics Institute decided to |