Samsung Bioepis Co., Ltd.
v.
Regeneron Pharmaceuticals, Inc.
IPR2023-00442

SAMSUNG BIOEPIS

Petition for *Inter Partes* Review of U.S. Patent No. 10,130,681

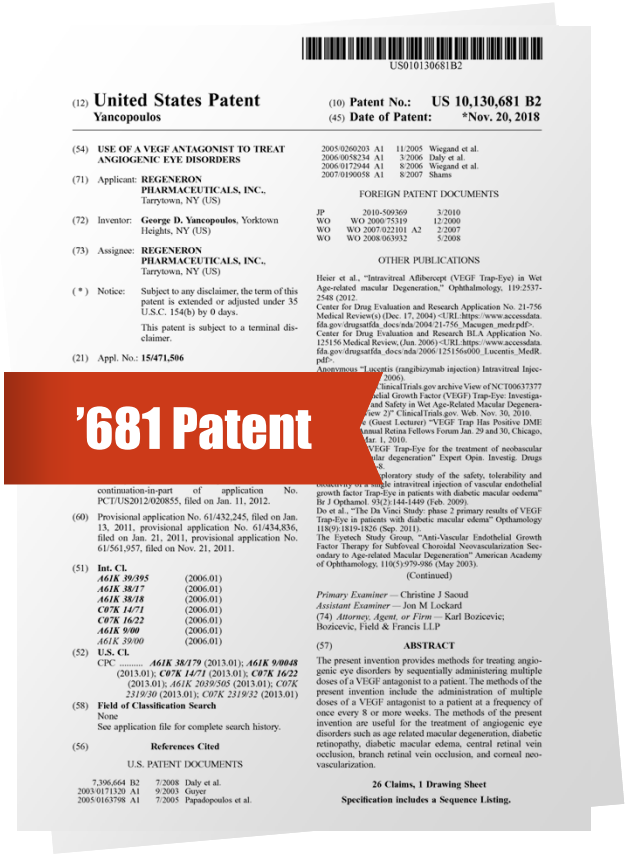
United States Patent and Trademark Office

April 19, 2024

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Samsung Bioepis Exhibit 1083

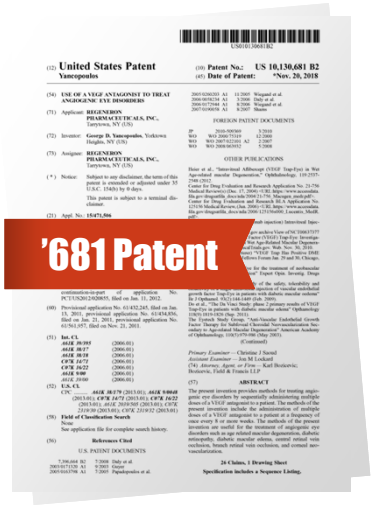
The ’681 Patent



- US 10,130,681 (“’681 Patent”)
- Title: USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS
- Assignee: Regeneron Pharmaceuticals, Inc. (“Regeneron”)
- Inventor: George D. Yancopoulos
- Earliest Possible Priority: January 13, 2011
- Filed: March 28, 2017
- Issued: November 20, 2018
- Challenged Claims: 1, 3-11, 13-14, 16-24, and 26

Ex. 1001; Pet., 8-11.

Representative Claim of the ’681 Patent



1. A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;

wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and

wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose;

wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule comprising (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2; (2) a VEGFR2 component comprising amino acids 130-231 of SEQ ID NO:2; and (3) a multimerization component comprising amino acids 232-457 of SEQ ID NO:2;

wherein exclusion criteria for the patient include all of:

(1) active intraocular inflammation;

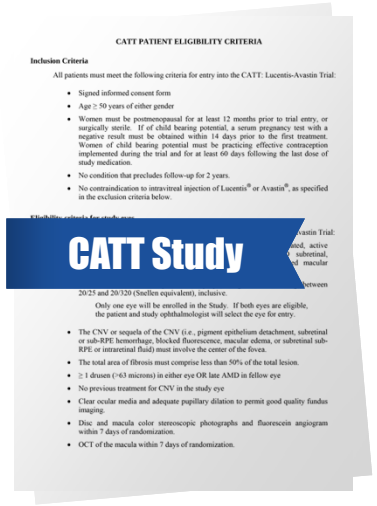
(2) active ocular or periocular infection;

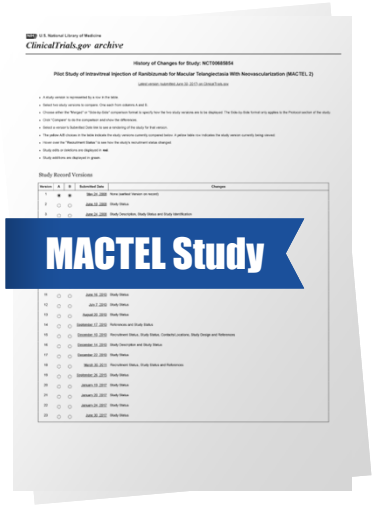
(3) any ocular or periocular infection within the last 2 weeks prior to treatment.

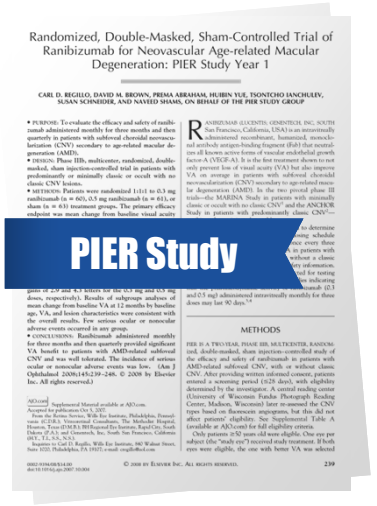
Ex. 1001; Pet., 11-13.

Grounds for All Challenged Claims









Dixon in view of CATT, MACTEL, and/or PIER Studies

35 U.S.C. § 103

Ex. 1006; Ex. 1031; Ex. 1032;
Ex. 1033; Ex. 1034; Pet., 8.

SAMSUNG BIOEPIS

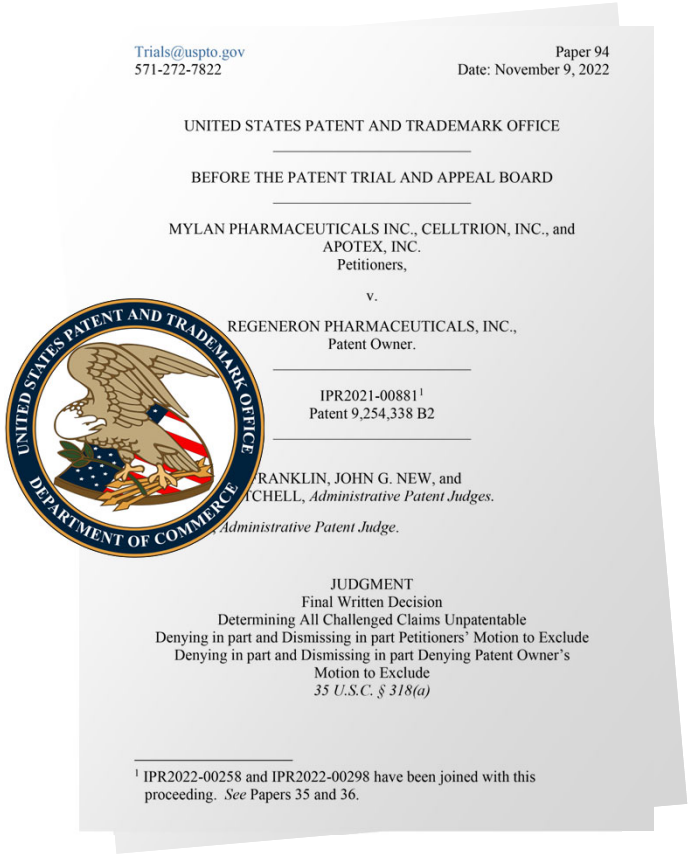
Dixon Discloses Claimed Dosing Regimen

Challenged Claims Identical to ’338 Patent Claims Except for Exclusion Criteria

Claim 1 of ’681 Patent	Claim 1 of ’338 Patent
1. A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;	1. A method for treating an angiogenic eye disorder in a patient, said method comprising sequentially administering to the patient a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;
wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and	wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose; and
wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose;	wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose;
wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule comprising (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2; (2) a VEGFR2 component comprising amino acids 130-231 of SEQ ID NO:2; and (3) a multimerization component comprising amino acids 232-457 of SEQ ID NO:2;	wherein the VEGF antagonist is a VEGF receptor-based chimeric molecule comprising (1) a VEGFR1 component comprising amino acids 27 to 129 of SEQ ID NO:2; (2) a VEGFR2 component comprising amino acids 130-231 of SEQ ID NO:2; and (3) a multimerization component comprising amino acids 232-457 of SEQ ID NO:2.
wherein exclusion criteria for the patient include all of: **(1) active intraocular inflammation;** **(2) active ocular or periocular infection;** **(3) any ocular or periocular infection within the last 2 weeks prior to treatment.**	

Ex. 1001; Ex. 1028, 14; Pet., 12-13.

PTAB Found Dixon Anticipates the Challenged Claims of the ’338 Patent



Trials@uspto.gov
571-272-7822

Paper 94
Date: November 9, 2022

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC., CELLTRION, INC., and APOTEX, INC.
Petitioners,

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner.

IPR2021-00881[1]
Patent 9,254,338 B2

RANKLIN, JOHN G. NEW, and
ICHELL, *Administrative Patent Judges.*

Administrative Patent Judge.

JUDGMENT
Final Written Decision
Determining All Challenged Claims Unpatentable
Denying in part and Dismissing in part Petitioners’ Motion to Exclude
Denying in part and Dismissing in part Denying Patent Owner’s Motion to Exclude
35 U.S.C. § 318(a)

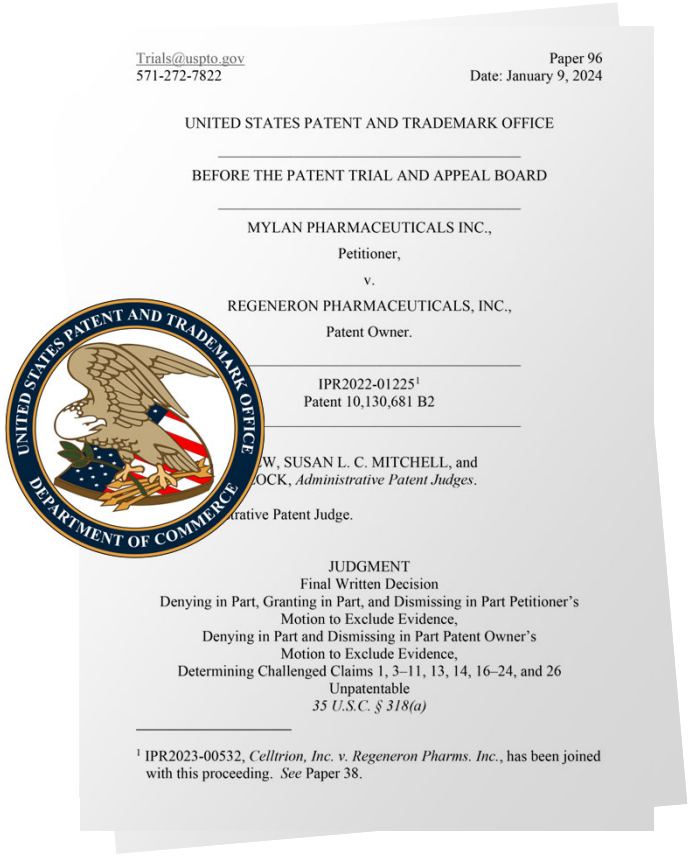
[1] IPR2022-00258 and IPR2022-00298 have been joined with this proceeding. *See* Papers 35 and 36.

- **IPR2021-00881 FWD: Dixon discloses the claimed dosing regimen of the ’338 patent**

> As noted above, Patent Owner does not dispute that Dixon discloses the remaining elements of independent claims 1 and 14, or the additional limitations of the challenged dependent claims. Based on the foregoing discussion and our consideration of record as a whole, we determine that Petitioners shown persuasively that Dixon discloses each element of independent claims 1 and 14, as well as the additional limitations of the challenged dependent claims. Accordingly, we determine that Petitioners have shown by a preponderance of the evidence that claims 1, 3–11, 13, 14, 16–24 and 26 are anticipated by Dixon.

Ex. 1004, 45; Pet., 16-17.

Giving No Patentable Weight to Exclusion Criteria, PTAB Found Dixon Anticipates Claims 1 and 14 of the ’681 Patent



Trials@uspto.gov
571-272-7822

Paper 96
Date: January 9, 2024

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.,

Petitioner,

v.

REGENERON PHARMACEUTICALS, INC.,

Patent Owner.

IPR2022-01225[1]
Patent 10,130,681 B2

…W, SUSAN L. C. MITCHELL, and
…OCK, *Administrative Patent Judges*.

…rative Patent Judge.

JUDGMENT
Final Written Decision
Denying in Part, Granting in Part, and Dismissing in Part Petitioner’s Motion to Exclude Evidence,
Denying in Part and Dismissing in Part Patent Owner’s Motion to Exclude Evidence,
Determining Challenged Claims 1, 3–11, 13, 14, 16–24, and 26 Unpatentable
35 U.S.C. § 318(a)

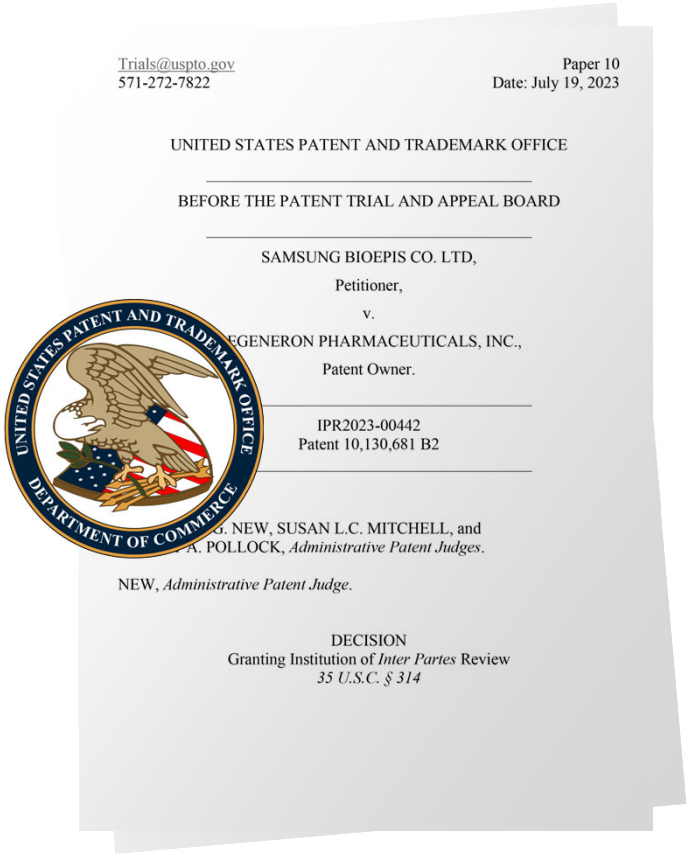
[1] IPR2023-00532, *Celltrion, Inc. v. Regeneron Pharms. Inc.*, has been joined with this proceeding. *See* Paper 38.

- **IPR2022-01225 FWD: PTAB again confirmed that Dixon discloses the claimed dosing regimen of the ’681 Patent**

> For the reasons explained in Section IV.A.3.d above, the exclusion criteria are entitled to no patentable weight. Because independent challenged claims 1 and 14 are otherwise identical to claims 1 and 14 of the ’338 patent of the -00881 Decision, we conclude, for the same reasons set forth in the -00881 Decision, that Petitioner has demonstrated, by a preponderance of the evidence, that challenged claims 1 and 14 of the ’681 patent are unpatentable as being anticipated by Dixon.

Ex. 1068, 60-61; Reply, 4, 18-19.

Institution Decision



Trials@uspto.gov
571-272-7822

Paper 10
Date: July 19, 2023

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SAMSUNG BIOEPIS CO. LTD,

Petitioner,

v.

EGENERON PHARMACEUTICALS, INC.,

Patent Owner.

IPR2023-00442
Patent 10,130,681 B2

G. NEW, SUSAN L.C. MITCHELL, and
A. POLLOCK, *Administrative Patent Judges*.

NEW, *Administrative Patent Judge*.

DECISION
Granting Institution of *Inter Partes* Review
35 U.S.C. § 314

- **Institution Decision incorporates by reference and adopts reasoning in FWD for '338 patent**

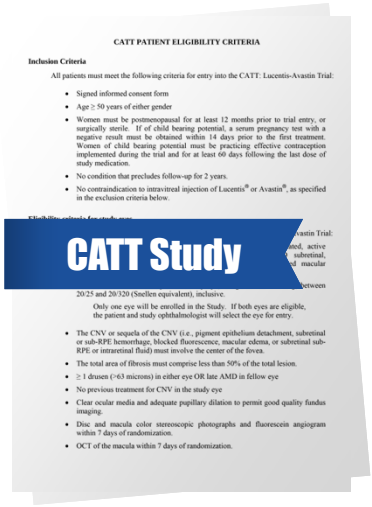
> As should be readily apparent to the reader, challenged claim 1 of the present Petition and claim 1 of the '338 patent are identical, with the sole exception in the '681 patent of the additional limitation reciting the exclusion criteria. Because, in the -00881 Decision, we concluded that claim 1 of the '338 patent is anticipated by Dixon, we incorporate here by reference and adopt our reasoning in the -00881 Decision with respect to the corresponding limitations of claim 1 of the '681 patent. *See* -00881 Decision, 26–46. We therefore conclude that Petitioner has demonstrated sufficiently that those limitations of claim 1 of the '681 patent are taught by Dixon.

Institution Decision, 15; Reply, 18.

SAMSUNG BIOEPIS

Exclusion Criteria Prior Art

CATT Study: July 2010



- **The CATT study evaluated the efficacy and safety of intravitreal injections of bevacizumab relative to ranibizumab**

EXCLUSION CRITERIA

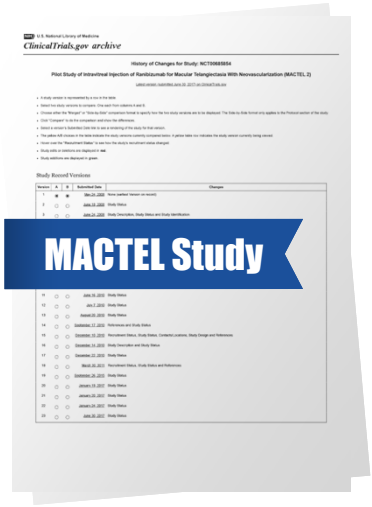
Subjects who meet any of the following criteria will be excluded from study entry:

Exclusionary Concurrent Ocular Conditions

- Any concurrent intraocular condition in the study eye (e.g., cataract or diabetic retinopathy) that, in the opinion of the investigator, could either require medical or surgical intervention during the 2 year follow-up period to prevent or treat visual loss that might result from that condition, or, if allowed to progress untreated, could likely contribute to loss of at least 2 Snellen equivalent lines of best corrected visual acuity over the 2 year follow-up period.
- Active or recent (within 4 weeks) intraocular inflammation (grade trace or above) in the study eye
- Current vitreous hemorrhage in the study eye
- History of rhegmatogenous retinal detachment or macular hole in the study eye
- History of vitrectomy in the study eye
- Active infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye
- Spherical equivalent of the refractive error in the study eye demonstrating more than 8 diopters of myopia

Ex. 1031, 6; Pet., 26-28; Reply, 9-10.

MACTEL Study: May 2008



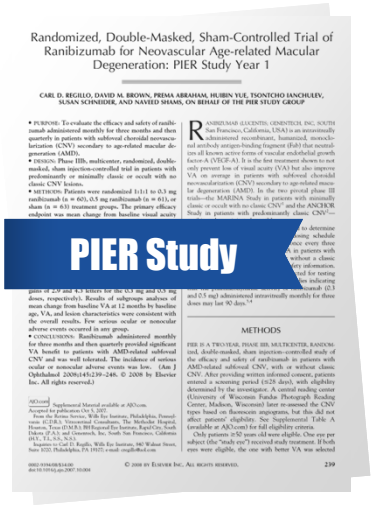
- **The MACTEL Phase II study was a pilot study for intravitreal injection of ranibizumab**

EXCLUSION CRITERIA:

- Safety and toxicity of ranibizumab have not yet been investigated in children. Further, it is unlikely that younger participants will be able to comply with all examinations and intravitreal injections. Therefore, participants below the age of 18 will be excluded from participation in the study. This ocular condition is not commonly found in participants below the age of 18.
- Participant has neovascularization in either eye.
- History (within past five years) or evidence of severe cardiac disease (apparent in electrocardiogram abnormalities, clinical history of unstable angina, acute coronary syndrome, myocardial infarction, revascularization procedure within six months prior to baseline, atrial or ventricular tachyarrythmias requiring ongoing treatment).
- History of stroke within 12 months of study entry.
- History within the past 30 days of a chronic ocular or periocular infection (including any history of ocular herpes zoster).
- Current acute ocular or periocular infection.
- Any major surgical procedure within one month of study entry.
- Known serious allergies to fluorescein dye.
- Previous participation in a clinical trial (for either eye) involving anti-angiogenic drugs (pegaptanib, ranibizumab, bevacizumab, anecortave acetate, Protein Kinase C inhibitors, etc.).
- Previous intravitreal drug delivery (e.g., intravitreal corticosteroid injection or device implantation) in the study eye.
- History of vitrectomy surgery in the study eye.
- History of glaucoma filtering surgery in the study eye.
- History of corneal transplant in the study eye.
- Pregnancy (positive pregnancy test) or lactation and premenopausal women not using adequate contraception. The following are considered effective means of contraception: surgical sterilization or use of oral contraceptives, barrier contraception with either a condom or diaphragm in conjunction with spermicidal gel, an IUD, or contraceptive hormone implant or patch.

Ex. 1032, 4; Ex. 1033; Pet., 28-30; Reply, 9-10.

PIER Study: February 2008



Exclusion Criteria

- Prior treatment with verteporfin photodynamic therapy, external-beam radiation therapy, or transpupillary thermotherapy in the study eye.
- Treatment with verteporfin photodynamic therapy in the nonstudy eye less than seven days preceding day zero.
- Previous participation in a clinical trial (for either eye) involving antiangiogenic drugs (pegaptanib, ranibizumab, anecortave acetate, protein kinase C inhibitors, etc.)
- Previous intravitreal drug delivery (e.g., intravitreal corticosteroid injection or device implantation) in the study eye.
- Previous subfoveal focal laser photocoagulation in the study eye.
- Laser photocoagulation (juxtafoveal or extrafoveal) in the study eye within one month preceding day zero.
- History of vitrectomy surgery in the study eye.

⋮

- Active intraocular inflammation (grade trace or above) in the study eye.
- Current vitreous hemorrhage in the study eye.
- History of rhegmatogenous retinal detachment or macular hole (stage 3 or 4) in the study eye.
- History of idiopathic or autoimmune-associated uveitis in either eye.
- Infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye.

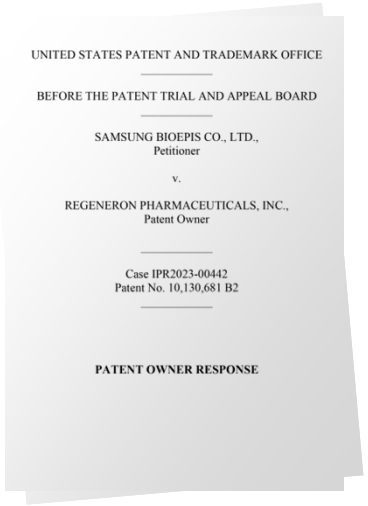
- **Evaluated the efficacy and safety of ranibizmab administered monthly for three months and then quarterly**

Ex. 1034, 13; Pet., 30-31; Reply, 9-10.

SAMSUNG BIOEPIS

Regeneron Proposed Claim Construction: Exclusion Criteria 2 and 3 (EC2/EC3)

Regeneron's Proposed Claim Construction: EC2 and EC3



UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SAMSUNG BIOEPIS CO., LTD.,
Petitioner

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner

Case IPR2023-00442
Patent No. 10,130,681 B2

PATENT OWNER RESPONSE

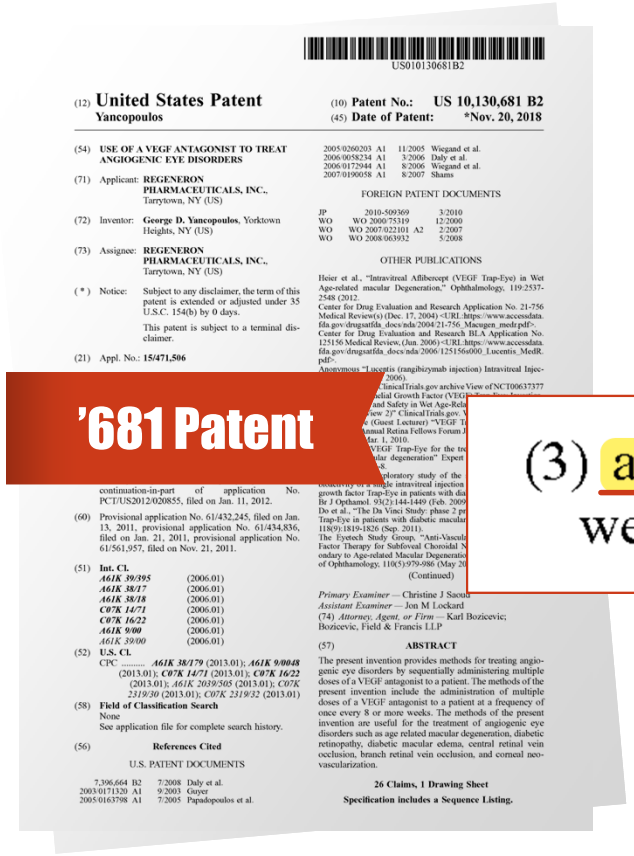
Regeneron Response

Claim term	PO's Proposed Construction
"(2) active ocular or periocular infection"	active, ongoing ocular or periocular infection
"(3) any ocular or periocular infection within the last 2 weeks prior to treatment"	any ocular or periocular infection within the last 2 weeks prior to treatment, which is no longer active at the time of treatment

- **Patent Owner's construction is contrary to plain language and unsupported by the specification**

POR, 8-20; Reply, 7-9.

Regeneron's Proposed Claim Construction: EC2 and EC3



US010130681B2

(12) **United States Patent**
Yancopoulos

(10) **Patent No.: US 10,130,681 B2**
(45) **Date of Patent: *Nov. 20, 2018**

(54) **USE OF A VEGF ANTAGONIST TO TREAT ANGIOGENIC EYE DISORDERS**

(71) Applicant: **REGENERON PHARMACEUTICALS, INC.**, Tarrytown, NY (US)

(72) Inventor: **George D. Yancopoulos**, Yorktown Heights, NY (US)

(73) Assignee: **REGENERON PHARMACEUTICALS, INC.**, Tarrytown, NY (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **15/471,506**

'681 Patent

(3) any ocular or periocular infection within the last 2 weeks prior to treatment.

- **Plain language of the claims and the specification does not support changes to claim language of EC3**
- **No guidance in specification for determining what "resolved" means in context**

Reply, 7-9.

Dr. Do's Testimony Regarding EC2 and EC3

111. By 2011, the POSA would have understood that to apply the Exclusion Criteria recited in the claims, a clinician would need to assess the patient to rule out the excluded conditions—active ocular inflammation, active ocular or periocular infection, and any ocular or periocular infection within the last 2 weeks prior to treatment. To do so, a clinician would examine the patient's eyes and take a medical history. This is because intraocular inflammation and ocular or periocular infection were known to have a range of presentations, certain of which would not be apparent absent examination by a trained clinician or, in the case of any ocular or periocular infection within the last 2 weeks prior to treatment, absent reporting by the patient or in the patient's medical records. *See, e.g.*, Ex.2120[30] at 6 (explaining that certain presentations of anterior uveitis—inflammation of the anterior chamber—are "apparent only on close examination"), *id.* at 7 (in intermediate uveitis, "the



Declaration of Dr. Diana V. Do

- **Dr. Do admitted that EC2 and EC3 are assessed in different ways**

Ex. 2056, ¶ 111; Reply, 8, 23.

Dr. Chaum Did Not Testify That EC2 and EC3 Are the Same



Deposition of Dr. Edward Chaum

Q How is that different -- let me ask it this way. How is that different from exclusion criteria number two, which is active ocular or periocular infection?

MR. SUMMERS: Objection to form.

THE WITNESS: In my view, it's not. It just defines a timeframe for the presence of infection.

BY MS. FISHMAN:

Q Okay. So you don't view exclusion criteria number two and exclusion criteria number three to be different?

MR. SUMMERS: Objection to form.

THE WITNESS: I think they're substantially the same from the perspective of the practitioner.

Ex. 2384, 122:18-24; Reply, 8-9; POR, 18-19.

Dr. Chaum Did Not Testify That EC2 and EC3 Are the Same



Deposition of Dr. Edward Chaum

Q Well, what is the basis for your statement that you understand exclusion criteria number three and exclusion criteria number two to be substantially the same?

A Well, as a practitioner, my goal is to demonstrate -- is to safely provide the care to that patient. And the presence of infection, whether it's active or recent, puts that patient at risk for increased risk of infection. Therefore, I would -- I would think of those two concepts of recent infection and active infection in a similar fashion, that they both put the patient at risk and would be a contraindication to potential treatment.

Ex. 2384, 123:7-19; Reply, 8-9.

SAMSUNG BIOEPIS

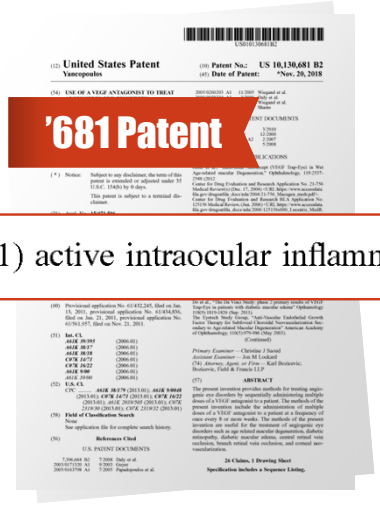
Obviousness of Exclusion Criteria

Obviousness of Exclusion Criteria – Summary

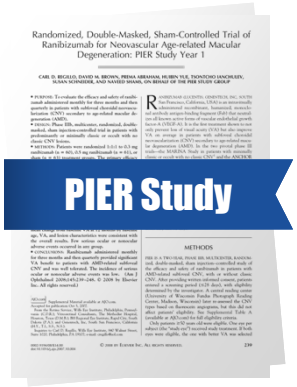
Exclusion Criteria	Exclusion Criteria from CATT, MACTEL, and PIER Studies
"(1) active intraocular inflammation"	"***Active intraocular inflammation*** (grade trace or above) in the study eye" Ex. 1034, PIER Study. "***Active*** or recent (within 4 weeks) ***intraocular inflammation*** (grade trace or above) in the study eye." Ex. 1031, CATT Study.
"(2) active ocular or periocular infection"	"***Current acute ocular or periocular infection***" Exs. 1032-1033, MACTEL Study "***Active infectious conjunctivitis, keratitis, scleritis, or endophthalmitis*** in either eye" Ex. 1031, CATT Study. "***Infectious conjunctivitis, keratitis, scleritis, or endophthalmitis*** in either eye" Ex. 1034, PIER Study.
"(3) any ocular or periocular infection within the last 2 weeks prior to treatment"	"***History within the past 30 days of a chronic ocular or periocular infection*** (including any history of ocular herpes zoster)" and "***Current acute ocular or periocular infection***" Exs. 1032-1033, MACTEL Study "Active or ***recent (within 4 weeks) intraocular inflammation*** (grade trace or above) in the study eye." Ex. 1031, CATT Study.

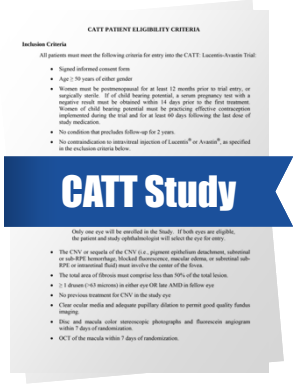
Pet., 43; Ex. 1002, ¶133; Ex. 1001.

CATT and/or PIER Render EC1 Obvious



(1) active intraocular inflammation;





Exclusion Criteria

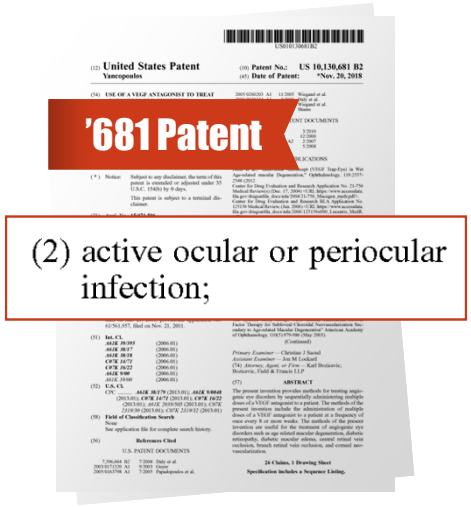
- Active intraocular inflammation (grade trace or above) in the study eye.
- Current vitreous hemorrhage in the study eye.
- History of rhegmatogenous retinal detachment or macular hole (stage 3 or 4) in the study eye.
- History of idiopathic or autoimmune-associated uveitis in either eye.
- Infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye.

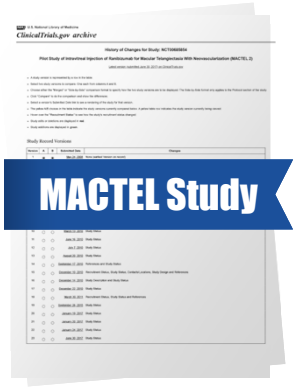
Exclusionary Concurrent Ocular Conditions

- Any concurrent intraocular condition in the study eye (e.g., cataract or diabetic retinopathy) that, in the opinion of the investigator, could either require medical or surgical intervention during the 2 year follow-up period to prevent or treat visual loss that might result from that condition, or, if allowed to progress untreated, could likely contribute to loss of at least 2 Snellen equivalent lines of best corrected visual acuity over the 2 year follow-up period.
- Active or recent (within 4 weeks) intraocular inflammation (grade trace or above) in the study eye

Ex. 1031, 6; Ex. 1034, 13; Pet., 41-52.

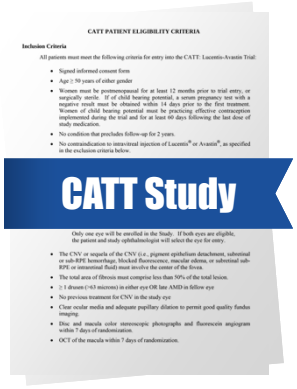
CATT, MACTEL, and/or PIER Render EC2 Obvious





EXCLUSION CRITERIA:

- Safety and toxicity of ranibizumab have not yet been investigated in children. Further, it is unlikely that younger participants will be able to comply with all examinations and intravitreal injections. Therefore, participants below the age of 18 will be excluded from participation in the study. This ocular condition is not commonly found in participants below the age of 18.
- Participant has neovascularization in either eye.
- History (within past five years) or evidence of severe cardiac disease (apparent in electrocardiogram abnormalities, clinical history of unstable angina, acute coronary syndrome, myocardial infarction, revascularization procedure within six months prior to baseline, atrial or ventricular tachyarrythmias requiring ongoing treatment).
- History of stroke within 12 months of study entry.
- History within the past 30 days of a chronic ocular or periocular infection (including any history of ocular herpes zoster).
- Current acute ocular or periocular infection.

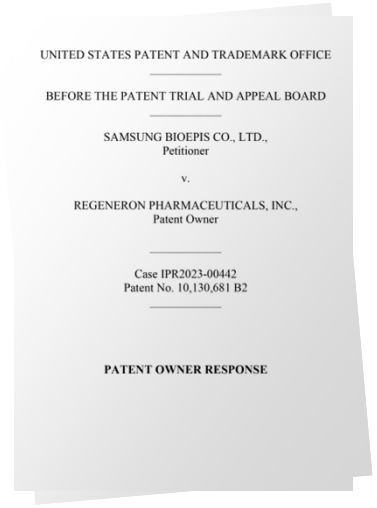


Exclusionary Concurrent Ocular Conditions

- Any concurrent intraocular condition in the study eye (e.g., cataract or diabetic retinopathy) that, in the opinion of the investigator, could either require medical or surgical intervention during the 2 year follow-up period to prevent or treat visual loss that might result from that condition, or, if allowed to progress untreated, could likely contribute to loss of at least 2 Snellen equivalent lines of best corrected visual acuity over the 2 year follow-up period.
- Active or recent (within 4 weeks) intraocular inflammation (grade trace or above) in the study eye
- Current vitreous hemorrhage in the study eye
- History of rhegmatogenous retinal detachment or macular hole in the study eye
- History of vitrectomy in the study eye
- Active infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye

Ex. 1031, 6; Ex. 1032, 4; Ex. 1033; Pet., 41-52.

No Dispute That CATT, MACTEL, and/or PIER Disclose EC1 and EC2



UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SAMSUNG BIOEPIS CO., LTD.,
Petitioner

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner

Case IPR2023-00442
Patent No. 10,130,681 B2

PATENT OWNER RESPONSE

Regeneron Response

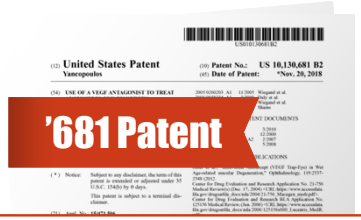
C. Petitioner Fails to Demonstrate Obviousness of All Claimed Exclusion Criteria

Every Challenged Claim of the '681 Patent incorporates the limitation: "wherein exclusion criteria for the patient include ***all of***: (1) active intraocular inflammation; (2) active ocular or periocular infection; (3) any ocular or periocular infection within the last 2 weeks prior to treatment." *See, e.g.*, Ex.1001, Claim 1, Claim 14. For Petitioner to meet its burden on obviousness, therefore, it must show that all limitations of the Challenged Claims, including all three Exclusion Criteria, would have been obvious to the POSA at the time of filing. Petitioner has failed in its burden with respect to at least EC3.

- **Patent Owner does not dispute that CATT, MACTEL, and/or PIER disclose EC1 and EC2**
- **Patent Owner only disputes EC3**

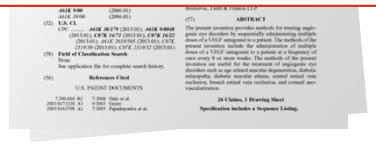
POR, 32-52; Pet., 41-44; Reply, 9-10.

MACTEL and/or CATT Render EC3 Obvious

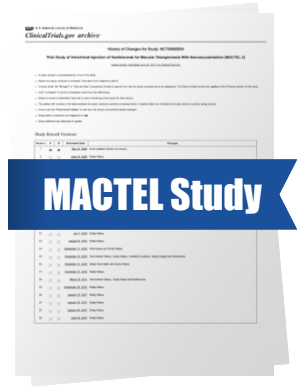


'681 Patent

(3) any ocular or periocular infection within the last 2 weeks prior to treatment.



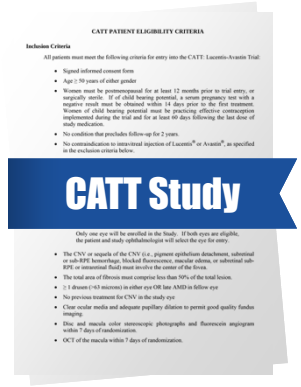
i.e., a recent infection anywhere on/in or surrounding the eye.



MACTEL Study

EXCLUSION CRITERIA:

- Safety and toxicity of ranibizumab have not yet been investigated in children. Further, it is unlikely that younger participants will be able to comply with all examinations and intravitreal injections. Therefore, participants below the age of 18 will be excluded from participation in the study. This ocular condition is not commonly found in participants below the age of 18.
- Participant has neovascularization in either eye.
- History (within past five years) or evidence of severe cardiac disease (apparent in electrocardiogram abnormalities, clinical history of unstable angina, acute coronary syndrome, myocardial infarction, revascularization procedure within six months prior to baseline, atrial or ventricular tachyarrythmias requiring ongoing treatment).
- History of stroke within 12 months of study entry.
- History within the past 30 days of a chronic ocular or periocular infection (including any history of ocular herpes zoster).
- Current acute ocular or periocular infection.



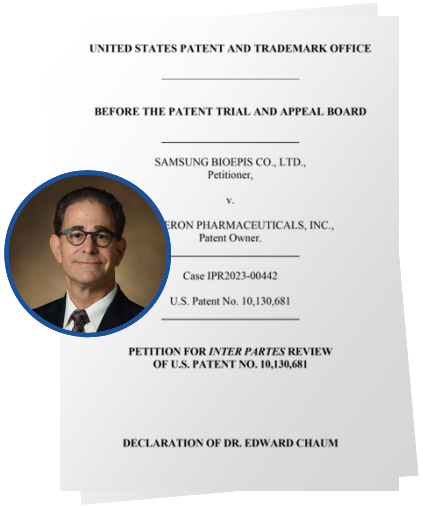
CATT Study

Exclusionary Concurrent Ocular Conditions

- Any concurrent intraocular condition in the study eye (e.g., cataract or diabetic retinopathy) that, in the opinion of the investigator, could either require medical or surgical intervention during the 2 year follow-up period to prevent or treat visual loss that might result from that condition, or, if allowed to progress untreated, could likely contribute to loss of at least 2 Snellen equivalent lines of best corrected visual acuity over the 2 year follow-up period.
- Active or recent (within 4 weeks) intraocular inflammation (grade trace or above) in the study eye

Ex. 1031, 6; Ex. 1032, 4; Ex. 1033; Pet., 41-52; Reply, 10.

MACTEL Renders EC3 Obvious


UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SAMSUNG BIOEPIS CO., LTD.,
Petitioner,

v.

[illegible]RON PHARMACEUTICALS, INC.,
Patent Owner.

Case IPR2023-00442

U.S. Patent No. 10,130,681

PETITION FOR *INTER PARTES* REVIEW
OF U.S. PATENT NO. 10,130,681

DECLARATION OF DR. EDWARD CHAUM

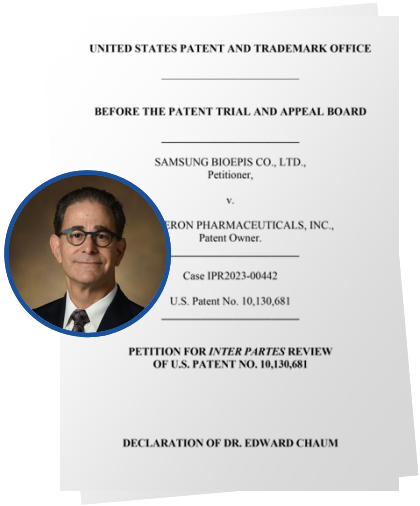
Declaration of Dr. Edward Chaum

142. Specifically, while a POSA would understand that "chronic" and "acute" do not generally have precise definitions in the art, the terms do not limit the type of ocular or periocular infection excluded, but rather generally refer to the length of time the infection is present. *See, e.g.* Exs. 1023-24, Ex. 1063. Excluding patients with a "history" of a chronic infection within the past 30 days (as well as any history of herpes zoster) would thus exclude any symptomatic infection in the past 14 days that was previously present long enough to be considered "chronic" (or which otherwise reoccurred); and excluding current "acute" infections would exclude any infections that had otherwise presented within a few weeks (i.e. one to three weeks) of treatment. *Id.*

- **MACTEL's criteria teach excluding chronic infections AND acute infections that are presented in the prior 1-3 weeks**

Ex. 1002, ¶¶140-149; Pet. 41-52; Reply, 11-12.

30 Days Includes 14 Days


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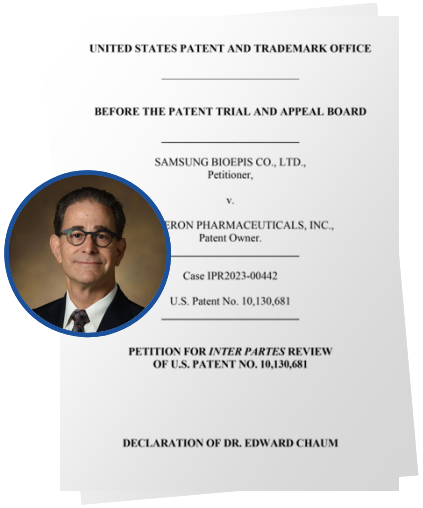
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142. Specifically, while a POSA would understand that "chronic" and "acute" do not generally have precise definitions in the art, the terms do not limit the type of ocular or periocular infection excluded, but rather generally refer to the length of time the infection is present. *See, e.g.* Exs. 1023-24, Ex. 1063. Excluding patients with a "history" of a chronic infection within the past 30 days (as well as any history of herpes zoster) would thus exclude any symptomatic infection in the past 14 days that was previously present long enough to be considered "chronic" (or which otherwise reoccurred); and excluding current "acute" infections would exclude any infections that had otherwise presented within a few weeks (i.e. one to three weeks) of treatment. *Id.*

- **A POSA would understand that excluding patients with a history of infection within the past 30 days would also exclude infection in past 14 days**
- **Claims are open-ended, reciting "exclusion criteria for the patient include…"**
- **Patent Owner identifies nothing non-obvious about 14 day exclusion period in view of 30-day exclusion period**

Ex. 1002, ¶¶141-142; Reply, 13-14; Pet. 45-52.

CATT Renders EC3 Obvious


UNITED STATES PATENT AND TRADEMARK OFFICE

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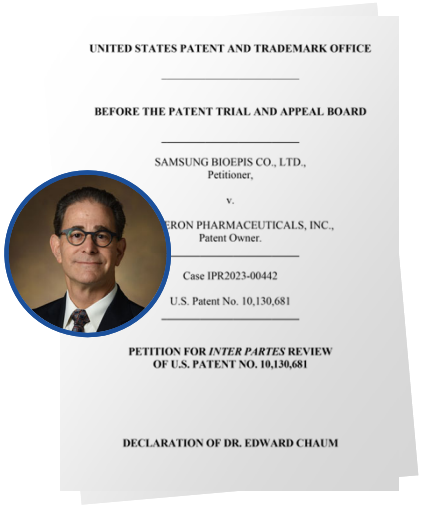
Declaration of Dr. Edward Chaum

139. This is also consistent with the CATT Study's exclusion for "[a]ctive or recent (within 4 weeks) intraocular inflammation (grade trace or above) in the study eye." *Id.* As noted above, recent inflammation was and is a known indicator for an active or recent ocular infection, and a POSA would have understood that one purpose of excluding those with active or recent trace inflammation was to exclude the possibility of an active or recent infection that might cause a complication, including endophthalmitis, which is a severe condition that can rapidly cause blindness.

- **CATT's disclosure of intraocular inflammation is a "hallmark" indicator for ocular and periocular infections**

Ex. 1002, ¶¶138-139; Pet. 45-53.

CATT and MACTEL Show Exclusion Criteria Are Basic Safety Precautions


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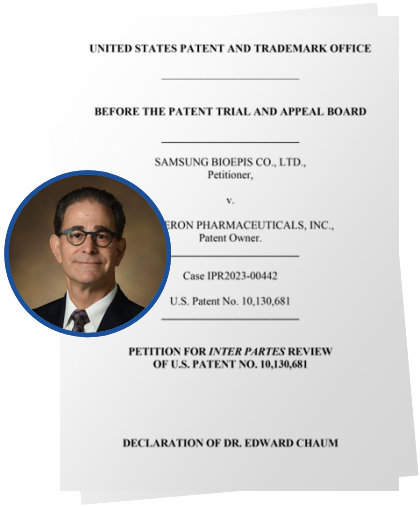
Declaration of Dr. Edward Chaum

146. I further note that a POSA would have understood that assessing for and excluding patients from treatment on the basis of these criteria was part of the standard of care. In my opinion, POSAs at the time understood that active intraocular inflammation and active or recent ocular or periocular infections made any intravitreal injection, such as those required by an intravitreally administered anti-VEGF dosing regimen, potentially unsafe. *See, e.g.* Ex. 1026 (Lucentis Label). Thus, it was the standard of care at the time to assess for active and recent infections and inflammation and to ensure they were cleared before intravitreal injections of anti-VEGF agents. The exclusion criteria recited in the '681 Patent reflect this practice.

- **EC3 and the other criteria were obvious as basic safety precautions taken as part of the standard of care, which are taught by the CATT and MACTEL exclusion criteria**

Ex. 1002, ¶¶146-60; Pet. 45-53.

A POSA Would Consider Exclusion Criteria for Intravitreally Injections


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Case IPR2023-00442

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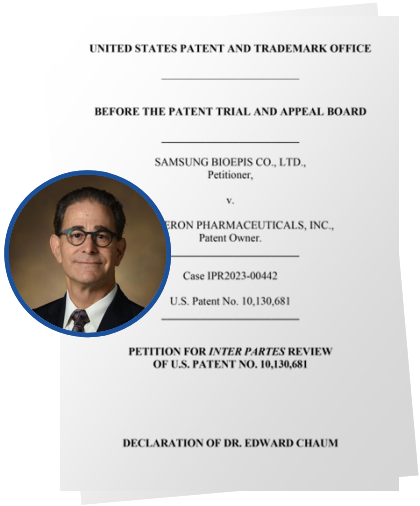
Declaration of Dr. Edward Chaum

132. In particular, the CATT, MACTEL, and PIER Studies (Exs. 1031-34) described above in Section IX.A, include the exclusion criteria for clinical trials of the leading intravitreally injected anti-VEGF treatments at the time—bevacizumab (Avastin®) and ranibizumab (Lucentis®). A POSA would have naturally considered them for evaluation of a method of treating a patient with an angiogenic eye disorder, including for their exclusion criteria. These exclusion criteria reflect basic safety precautions that were standard in the art.

- **A POSA would have been motivated to look at exclusion criteria from prior clinical trials for intravitreally injected drugs**
- **The claimed exclusion criteria were used in trials of each of the major intravitreally injected drugs at the time and demonstrate the standard of care**

Ex. 1002, ¶¶130-160; Pet. 48-53.

Intravitreal Injections As a Method Would Have Motivated a POSA to Adopt EC1-EC3


UNITED STATES PATENT AND TRADEMARK OFFICE

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[illegible]RON PHARMACEUTICALS, INC.,
Patent Owner.

Case IPR2023-00442

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PETITION FOR *INTER PARTES* REVIEW
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DECLARATION OF DR. EDWARD CHAUM

Declaration of Dr. Edward Chaum

156. Second, POSAs also would have been motivated to adopt these exclusion criteria from the CATT, MACTEL, and PIER Studies in the context of treating with aflibercept specifically. That is because these studies evaluated Lucentis® (ranibizumab) and Avastin® (bevacizumab), the leading anti-VEGF agents injected intravitreally at the time. Moreover, a POSA would have understood that it was method of administration—intravitreal injection—not the specific anti-VEGF agent being administered that raised the patient safety concerns. Thus, a POSA applying the dosing regimen of Dixon would be motivated consider the exclusion criteria from these other studies involving intravitreal injection of related anti-VEGF drugs, which raised the same safety concerns as the prior intravitreal injections of anti-VEGF agents.

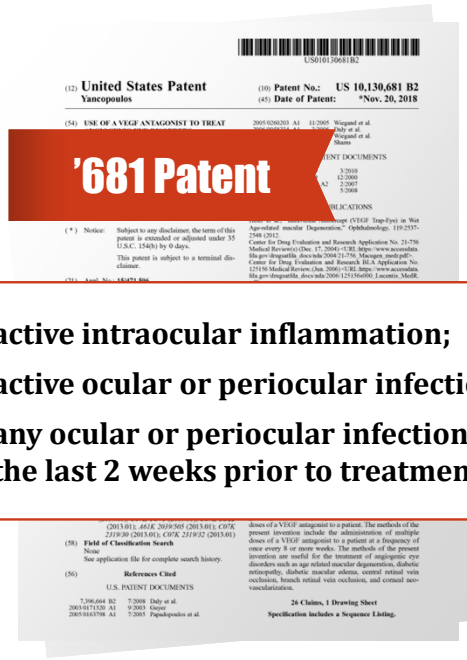
- **A POSA would have understood intravitreal injections as a method, regardless of injectable, raised safety concerns**
- **A POSA would have been motivated to consider EC from other studies involving intravitreal injections**

Ex. 1002, ¶¶156, 61; Pet. 48-53; Reply 14-15.

SAMSUNG BIOEPIS

Secondary Considerations

The Eylea Label Does Not Practice the '681 Claimed Method

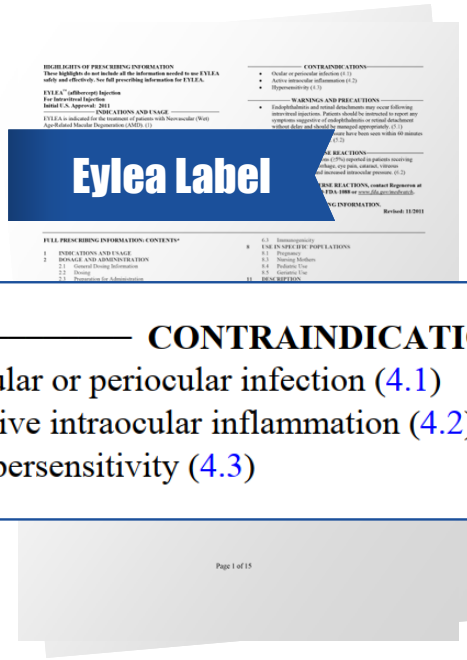


(1) active intraocular inflammation;

(2) active ocular or periocular infection;

(3) any ocular or periocular infection within the last 2 weeks prior to treatment.

≠



CONTRAINDICATIONS

- Ocular or periocular infection (4.1)
- Active intraocular inflammation (4.2)
- Hypersensitivity (4.3)

Does not disclose EC3 or direct exclusion of relevant patients

Ex. 1001; Ex. 2056, ¶184; Ex. 1062, 1; Reply, 23-26.

Dr. Do Did Not Cite the Eylea Label When Describing Alleged Practice of EC1-3

> The parties also agree that the Exclusion Criteria are mandatory—not optional—and require assessment of the patient. Ex.2056, ¶¶110-116; Ex.1002, ¶146; Ex.2384

Regeneron Patent Owner Response

> It is rare that patients present with active ocular or periocular infection, active intraocular inflammation, or history of prior ocular or periocular infection within the last two weeks—such issues arise only in less than 2% of cases. When this does happen, I determine whether to administer the intravitreal injection of the VEGF antagonist, or whether to wait, and treat the condition, if needed. In certain of these cases, less than 1%, I do determine to withhold the injection (i.e., exclude the patient from treatment, at least temporarily). In other cases, I may proceed with the intravitreal injection despite the presence of one of these conditions, but in these cases, I am not performing the claimed methods.

Dr. Diana Do Declaration



POR, 18; Ex. 2056, ¶184; Ex. 1062; Reply, 23-26.

No Nexus Between Evidence and Merits of Claimed Invention



"In evaluating whether the requisite nexus exists, the identified objective indicia must be directed to what was not known in the prior art—including patents and publications—which may well be the novel combination or arrangement of known individual elements."

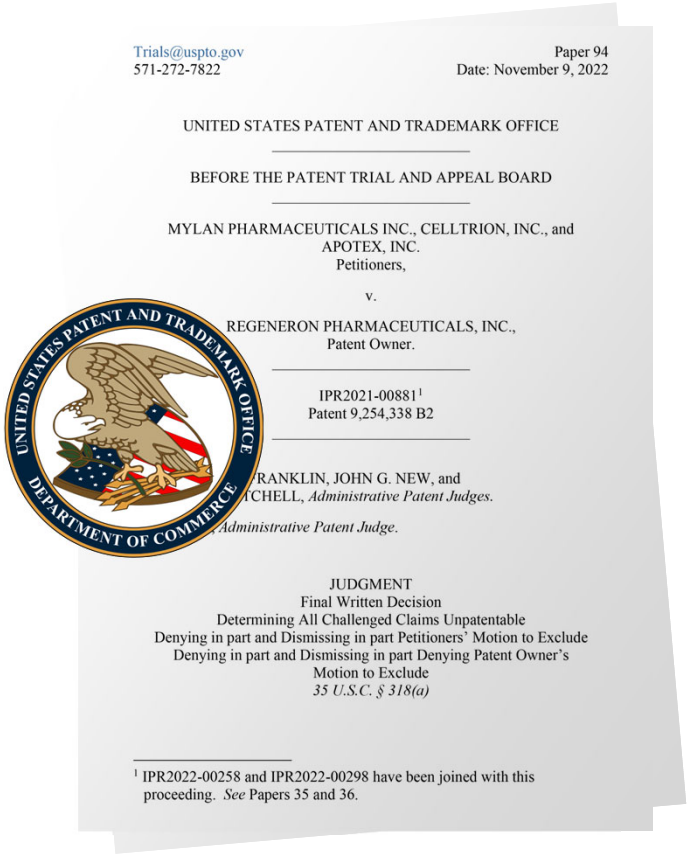
Novartis AG v. Torrent Pharms. Ltd.,
853 F.3d 1316, 1331 (Fed. Cir. 2017)

Petition, 55.

SAMSUNG BIOEPIS

Claim Construction: Method of Treatment

Regeneron's Proposed Claim Constructions: Preamble



Trials@uspto.gov
571-272-7822

Paper 94
Date: November 9, 2022

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC., CELLTRION, INC., and APOTEX, INC.
Petitioners,

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner.

IPR2021-00881[1]
Patent 9,254,338 B2

RANKLIN, JOHN G. NEW, and
ICHELL, *Administrative Patent Judges.*

Administrative Patent Judge.

JUDGMENT
Final Written Decision
Determining All Challenged Claims Unpatentable
Denying in part and Dismissing in part Petitioners' Motion to Exclude
Denying in part and Dismissing in part Denying Patent Owner's Motion to Exclude
35 U.S.C. § 318(a)

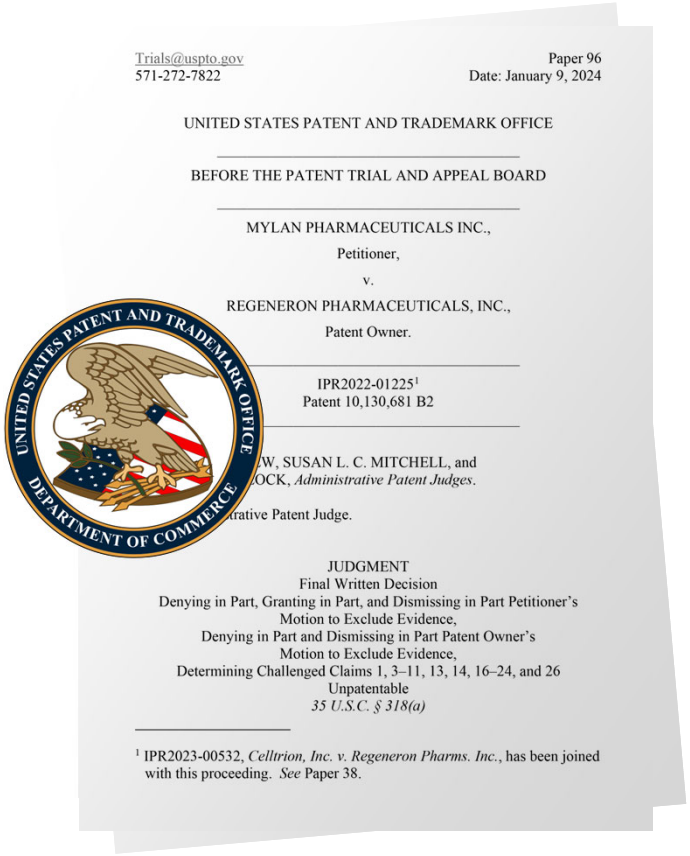
[1] IPR2022-00258 and IPR2022-00298 have been joined with this proceeding. *See* Papers 35 and 36.

- **PTAB rejected argument that claims require "high level of efficacy" in IPR for '338 patent**

> Based on the foregoing and our review of the record as a whole, we find no persuasive support for construing the preamble recitation of a "method for treating a patient with an angiogenic eye disorder" as requiring such "treating" to achieve any particular level of effectiveness, much less a "high level of efficacy." Rather, as discussed above, we find that the evidence of record and the Specification support construing the phrase as meaning administering a compound, i.e., the recited VEGF antagonist, to such patient for the purpose of improving or providing a beneficial effect in their angiogenic eye disorder.

Ex. 1004, 17-23; Pet., 16-17.

Regeneron's Proposed Claim Constructions: Preamble



Trials@uspto.gov
571-272-7822

Paper 96
Date: January 9, 2024

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.,

Petitioner,

v.

REGENERON PHARMACEUTICALS, INC.,

Patent Owner.

IPR2022-01225[1]
Patent 10,130,681 B2

W, SUSAN L. C. MITCHELL, and
OCK, *Administrative Patent Judges*.

rative Patent Judge.

JUDGMENT
Final Written Decision
Denying in Part, Granting in Part, and Dismissing in Part Petitioner's Motion to Exclude Evidence,
Denying in Part and Dismissing in Part Patent Owner's Motion to Exclude Evidence,
Determining Challenged Claims 1, 3–11, 13, 14, 16–24, and 26 Unpatentable
35 U.S.C. § 318(a)

[1] IPR2023-00532, *Celltrion, Inc. v. Regeneron Pharms. Inc.*, has been joined with this proceeding. *See* Paper 38.

- **PTAB rejected argument for second time in prior IPR for '681 patent**

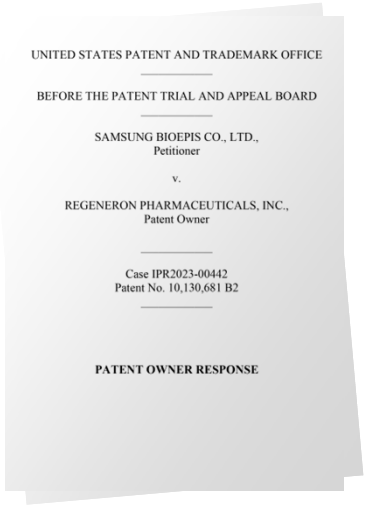
> We adopt the same reasoning here, and find that, for the purposes of this Decision, the evidence of record and the Specification support construing the preamble's recitation of a "method for treating a patient with an angiogenic eye disorder" as meaning administering a compound, i.e., the recited VEGF antagonist, to such patient for the purpose of improving or providing a beneficial effect in their angiogenic eye disorder. We find that, as in *Eli Lilly*, although the claims "encompass a clinical result, they do not require such a result." *Eli Lilly*, 8 F.4th at 1343. We consequently reject Patent Owner's argument that the preamble to the challenged claims requires a "high level of efficacy," as proposed by Patent Owner. *See* Ex. 3001, 22.

Ex. 1068, 33-37; Reply, 4.

SAMSUNG BIOEPIS

Reasonable Expectation of Success

Patent Owner's RES Argument Hinges on Reading in Efficacy Requirement



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Case IPR2023-00442
Patent No. 10,130,681 B2

PATENT OWNER RESPONSE

Regeneron Response

> Here, where the preamble is limiting and requires "administration of the VEGF antagonist" "***for the purpose*** of providing an improvement of or a beneficial effect on the[] angiogenic eye disorder" (Pet., 20 (emphasis original)), Petitioner must show that the POSA had a reasonable expectation that administering VEGF Trap-Eye on the claimed dosing regimen would "treat[]" the disorder (*id.*)—*i.e.*, achieve and maintain standard-of-care efficacy. Petitioner cannot make this showing.

POR, 22-32; Reply, 20-22.

Efficacy Not Required for Obviousness



"Conclusive proof of efficacy is not necessary to show obviousness. All that is required is a reasonable expectation of success."

Hoffmann-La Roche Inc. v. Apotex Inc.,
748 F.3d 1326, 1331 (Fed. Cir. 2014).

Reply, 20-22.