THIRD PARTY SPONSORED / INVESTIGATOR INITIATED INTERVENTIONNAL TRIAL AGREEMENT

BY AND BETWEEN

NOVARTIS KOREA LTD.

AND

WONKWANG UNIVERSITY HOSPITAL

STUDY TITLE :

Effects of Intravitreal Ranibizumab for Macular Edema With Nonproliferative Dibetic retinopathy

(NCT02834663 / CRFB002DKR03T)

Study Protocol

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THIRD PARTY SPONSORED / INVESTIGATOR INITIATED TRIAL AGREEMENT

This Third Party Sponsored/Investigator Initiated Trial Agreement ("**Agreement**") is entered into by and between Novartis Korea Ltd., 18Fl, Yonsei Severance B/D, 10 Tongil-ro, Joong-gu, Seoul, 04527, Korea ("**Novartis**") and [Institution], [Wonkwang University Hospital, located at [Muwang-ro 895 Wonkwang Univ. Hospital, Dept. of Ophthalmolgy, Iksan city, Jeonbuk South Korea]] ("**Sponsor**") and [Prof. Yun-Sik Yang], [Dept. of Ophthalmology, Wonkwang University Hospital], located at [Muwang-ro 895 Wonkwang Univ. Hospital, Dept. of Ophthalmolgy, Iksan city, Jeonbuk South Korea] ("**Principal Investigator**")

WHEREAS, the Sponsor has proposed and is willing to undertake a clinical trial known as [Effects of Ranibizumab to delay or regression non-proliferative diabetic retinopathy(NPDR) with DME assessed by microaneurysm changes: A pilot study] (the "**Study**"), such Study to be carried out at the Sponsor and/or at the Participating Sites;

WHEREAS, the Sponsor has assumed responsibility for the initiation, management and financing of the Study and will be the sponsor of the Study for the purpose of the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice ("**ICH GCP**") and the Good Clinical Practice guidelines under Pharmaceutical Affairs Act of Korea (the "**KGCP**");

WHEREAS, Novartis is interested in the scientific outcome of the Study and the scientific implications of the future development of ***[Lucentis]*** ®; and

WHEREAS, at the Sponsor's request, Novartis has agreed to provide funding for the Study and/or provide supplies of ***[Lucentis]*** ®; and provide such information, advice and assistance as may be required during the course of the Study and agreed between the parties on the terms and conditions set out in this Agreement; and

WHEREAS, the Principal Investigator and the Sponsor have agreed to conduct the Study on the terms and conditions set out in this Agreement.

NOW, THEREFORE, the parties have agreed as follows:

1. DEFINITIONS

The following definitions shall apply:

"**Affiliate**" means, with respect to a party, any corporation or other business entity controlled by, controlling or under common control with that party. "Control" for the purposes of this definition shall mean direct or indirect beneficial ownership of fifty percent (50%) or more of the voting interest in an entity, or such other relationship as, in fact, constitutes actual control.

"**Applicable Laws**" means all laws, regulations, orders and guidelines applicable to the conduct of the Study and the processing of Personal Data, including Personal Information Protection Act of Korea ICH GCP, and the applicable version of the World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects.

"**Intellectual Property**" means all patents, design rights (whether registered or unregistered), trademarks, service marks, domain names, trade and business names,

publicly available and registered applications for any of the foregoing, copyrights, inventions, Information, trade secrets, know-how and registered database rights including all applications for the same, all extensions and renewals to any of them and publicly available and registered applications for any of them and any right or form of protection of a similar nature and having equivalent or similar effect to any of them which may subsist anywhere in the world.

"**Invention**" means all discoveries, improvements, inventions, new concepts and ideas arising from the Study together with all related results and information.

"**Novartis Information**" means technical knowledge, know-how, experience, data and business background of a confidential nature provided by Novartis under this Agreement.

"**Novartis Intellectual Property**" has the meaning set forth in Section 11.1.

"**Participating Sites**" means any clinical site which is participating in the performance of the Study.

"**Personal Data**" means any information that identifies or can identify a specific individual, that is collected, accessed, received, transmitted, maintained or used directly or indirectly, in connection with the Study.

"**Principal Investigator**" means ***[***Prof. Yun-Sik Yang***]*** who will be responsible for the direction of the Study in accordance with applicable Sponsor policies.

"**Protocol**" means the Study protocol, a signed copy of which shall be attached at Annex 1, and any amendments thereto.

"**Sponsor**" means an individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial.

"**Sponsor Intellectual Property**" has the meaning set forth in Section 11.2.

"**Study Data**" means the information that is collected as part of the Study.

"**Study Drug**" means ***[Lucentis]***

"**Subcontractor**" means any party who has been contracted by the Sponsor to perform part of the Study or provide goods or services in support thereof.

2. TERM OF THE AGREEMENT

This Agreement becomes effective upon signature by both parties ("**Effective Date**") and will remain in effect until the Study has been completed and the Sponsor has provided Novartis with a copy of the final study report, unless terminated earlier pursuant to the provisions of this Agreement.

3. RESPONSIBILITY OF THE SPONSOR

3.1 The Sponsor shall be the sole sponsor of the Study. Prior to initiating the Study , the Agreement shall be fully executed and include the final Protocol in Annex 1, which has been previously submitted by the Sponsor in English , to Novartis for Novartis' review for

the purpose of confirming its scientific soundness. If the Protocol is not in English, the Protocol synopsis in English shall be attached to the Agreement in addition to the Protocol.

3.2 For purposes of the Study, Sponsor shall be the personal data controller (as defined in Article 2, Item 5 of the Personal Information Protection Act of Korea) and is solely responsible for adherence to all data protection laws as they relate to the Study.

3.3 The Sponsor shall:

(a) Ensure that the Study is conducted in compliance with this Agreement, the Protocol and with all Applicable Laws, including ICH GCP;

(b) Obtain all necessary approvals from an appropriate ethics committee and competent regulatory authorities prior to starting the Study and maintain such approvals for the duration of the Study;

(c) Procure that Participating Sites obtain the written informed consent of each subject or patient enrolled in the Study;

(d) Control the scientific and technical conduct of the Study;

(e) Retain all records resulting from the Study ("Records") for the time required by ICH GCP and other Applicable Laws;

(f) procure that Participating Sites receive, store and use the Study Drug(s) in accordance with Applicable Laws; and

(g) Be responsible for the management and payment of all Participating Sites and any Subcontractors engaged by the Sponsor.

3.4 Throughout the term of this Agreement the Sponsor shall allow Novartis and its agents to visit the facilities where the Study is performed; including third party sites, to audit the facilities and Records, to review documents and to interview relevant personnel, to assure Novartis the Study is being and has been conducted in compliance with this Agreement, the Protocol and with all Applicable Laws. Such audit shall take place during normal business hours and upon reasonable advance notice to Sponsor. Novartis shall notify Sponsor in writing of any observations or findings of non-compliance and the Parties shall agree on corrective action to be implemented, which action shall be implemented at Sponsor's expense. The Sponsor agrees to inform Novartis immediately in case of an inspection of the Study announced by national or foreign health authorities and to allow any such health authorities to inspect the Records. Auditing by Novartis or its agents shall be performed in accordance with Applicable Laws.

3.5 The Study shall be carried out under the supervision of the Principal Investigator. In the event that the Principal Investigator ceases to be involved in the Study for whatever reason, the Sponsor agrees to notify Novartis immediately. Within thirty (30) days after such notification the Sponsor and Novartis shall agree a successor who has similar clinical expertise and similar experience, and who is acceptable to both parties. The new Principal Investigator shall sign an amendment to the Agreement to ensure he complies with the terms of the Agreement. The key contacts of Novartis and the Sponsor for matters related to the Study shall be as specified in **Annex 2** (Key Contacts).

3.6 The Sponsor shall be responsible for the management and payment of all Participating Sites and Subcontractors engaged by the Sponsor. It is the responsibility of the Sponsor to ensure that all work performed by Subcontractors is done in compliance with this

Agreement and to provide Subcontractors with all necessary documentation to allow the proper performance of the Study, including but not limited to Investigator's Brochure, the Study Product Monograph and locally approved Study Product Information, if applicable. The Sponsor undertakes to impose on all Subcontractors terms and conditions not less strict than those set out in this Agreement, including, but not limited to provisions contained in Section 3.4 (concerning auditing rights), Annex 5 (Safety Data collection and reporting responsibilities), Section 7 (Publication), Section 9 (Confidentiality), Section 10 (Ownership of Data), Section 10.3 (concerning Novartis' access right to the Study Data), Section 11 (Intellectual Property) and Section 28.1 (Sponsor's Indemnity Obligations)]. The Sponsor agrees that to the extent the terms of any current or future executed contract between the Sponsor and any Subcontractor and the terms of this Agreement conflict, the terms of this Agreement shall govern. The Sponsor shall be liable to Novartis for any breach of those obligations by any Subcontractor.

3.7 The Sponsor shall keep designated Novartis personnel fully informed of the progress of the Study. In particular, the Sponsor will provide Novartis ***[monthly]*** and at any other time upon Novartis' written request with progress reports, which will include the following information and any other information that Novartis may reasonably request:

- ❑ general study progress, milestones and overall enrollment/recruitment status
- ❑ demographics of study patients (age, gender)
- ❑ total number of patients who have discontinued study medication
- ❑ confirmation that all Serious Adverse Event (SAE) reports, reports of drug exposure during pregnancy in patients exposed to the Novartis Study Drug and reports of Novartis Study Drug misuse or abuse, collected from the Study to date, have been transferred to Novartis

3.8 The Sponsor shall report SAEs and other safety information to Novartis in accordance with the procedures set out in Annex 5.

3.9 The Sponsor shall notify Novartis of any significant amendment made to the Protocol prior or during the conduct of the Study, and of any non-routine communications with any ethics committee or health authority prior to or during the conduct of the Study. A significant amendment to the Protocol (hereinafter a "Significant Amendment") shall be defined as any modification to the Protocol which may impact the conduct of the study, the scientific value of the Study, the potential benefit of the patient or patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects requiring a formal amendment to the Protocol. If, in the Principal Investigator's opinion, it is necessary to make a Significant Amendment to the Protocol during the Study, the Sponsor will immediately inform Novartis prior to submission to any ethics committee or health authority. If the amendments made to the Protocol substantially change or alter the original proposal approved by Novartis, Novartis reserves the right to early terminate the Agreement according to Section 13.2.

3.10 The Sponsor shall provide Novartis promptly with copies of all interim reports produced during the performance of the Study and shall also provide Novartis with a copy of the final study report ("TPSR") produced at the end of the Study which includes a full summary of safety and efficacy information from the Study as soon as the report is finalized preferably within nine (9) months of the last visit by the last patient ("**LPLV**") but no later than 13 months after completion of the Study. If the Study includes pediatric patients, the TPSR shall be provided within four (4) months from LPLV but no later than seven (7) months after completion of the Study. The final study report shall comply with the established principles and standards for the corresponding format according to ICH GCP and shall be in English.

3.11 The Sponsor shall independently prepare and submit publication(s) reporting study results to scientific congress and/or journal. Sponsor shall provide Novartis the publication draft prior to submission/presentation, and the final presented or published version as outlined in Section 7. The final publication shall be provided within twenty-four (24) months from LPLV.

4. RESPONSIBILITY OF NOVARTIS

4.1 Novartis has agreed to provide financial support for the Study in the maximum amount of (79,063,000 KRW / Seventy-nine million, sixty three thousand KRW Payment shall be made by Novartis according to the Payment Plan set forth in **Annex 3**.

4.2 Payment will be made by Novartis within sixty (60) days of receipt of invoices from the Sponsor, according to the Payment Plan detailed in Annex 3. Such invoices shall reflect the amounts stated in Section 4.1 and shall bear the reference code: XXXX

Invoices shall be submitted to the following address:

Novartis Korea Ltd.

18Fl. Yonsei Severance B/D, 10 Tongil-ro, Joong-gu, Seoul, 04527, Korea

4.3 No payments other than those explicitly foreseen under Section 4.1 shall be made by Novartis to the Sponsor with respect to the Study unless agreed in writing (excluding writings exchanged by e-mail). Such agreement must be executed by authorized personnel, must include a specific statement of any fees or costs to be paid and the reasons for payment, and must be attached as an Annex to this Agreement.

4.4 Novartis shall provide the Sponsor with an updated Investigator's Brochure, product monograph, or locally approved product information. The Sponsor will receive the updated Investigator's Brochure in accordance with the timelines as defined in Novartis SOPs.

4.5 Novartis shall provide the Sponsor with appropriate safety information related to the Study Drug in accordance with the procedures set out in Annex 5.

4.6 Novartis shall supply the Sponsor with sufficient supplies of the Study Drug to conduct the Study in accordance with the procedures set out in Annex 4.

5. PUBLIC STATEMENTS

5.1 Each party shall have the right to make public disclosure of its involvement in the Study. The disclosing party will provide the other party with such proposed public statement or press release within a reasonable time prior to the planned disclosure.

5.2 The non-disclosing party shall have the right to give comments and suggestions for modification of such public statements or press releases, and the disclosing party agrees to consider and discuss such comments and suggestions with the other party in good faith. The disclosing party agrees to accept such comments and suggestions to the extent based on confidentiality of information or patent protection concerns. The non-disclosing party will not request more than one (1) month for such review.

5.3 The Sponsor shall register the Study and post Study Results on ClinicalTrials.gov and/or one or more other Internet clinical trial registries in accordance and compliance with all applicable laws and regulations and the requirements and guidelines of each Internet clinical trial registry on which the Clinical Trial will be posted. Each such posting shall

comply with all applicable requirements of this Agreement including, but not limited to, Sections 5 and 9; however, to the extent that Section 5.2 is deemed to require Novartis' consent for any such posting, such consent is hereby given. Novartis will not register the Study, nor post Study Results on ClinicalTrials.gov and/or any other Internet clinical trial registry.

6. SPONSOR's CONSENT TO REPORTING TO CMS (APPLICABLE TO U.S. LICENSED HEALTH CARE PROVIDERS AND US TEACHING HOSPITALS)

6.1 If Sponsor has an active license to practice medicine in a state of the U.S. (irrespective of whether Sponsor is domiciled or primarily practicing in a state of the U.S.) or is in the process of applying for such a license ("U.S.-licensed Health Care Provider") or a U.S. Teaching Hospital (as identified by the U.S. Centers of Medicare and Medicaid Services ("CMS")), Sponsor understands and agrees that Novartis will process certain personal data pertaining to Sponsor and/or the activities related to the conduct of the Study under this Agreement and, in particular, transfer such personal data to the CMS, a government agency in the U.S. This personal data may be obtained directly from Sponsor or from third parties.

6.2 In particular, if Sponsor is a U.S.-licensed Health Care Provider or a U.S. Teaching Hospital (as identified by the CMS), Sponsor acknowledges and agrees to the following:

(a) Novartis will process and, in particular, transfer to CMS, personal data relating to Sponsor and to the activities performed by Sponsor under this Agreement, including without limitation, Sponsor's name, city and state of residence or business (as applicable), the Sponsor's specialty, the National Provider Identifier (NPI), the nature of the Services performed pursuant to this Agreement, and any and all payments, reimbursements for expenses or other transfers of value made in other than money form relating to this Agreement ("Sponsor Data"); and

(b) The Sponsor Data transferred to CMS by Novartis will no longer be controlled by Novartis and will be publicly disclosed by CMS in accordance with the U.S. Physicians' Payment Sunshine Act and its regulations. Once the Sponsor Data has been transferred to CMS, Novartis cannot guarantee and is no longer responsible for the privacy and data protection of the Sponsor's Data transferred to CMS.

7. PUBLICATION

7.1 The Sponsor shall independently prepare and submit the study-related publications to scientific congresses and/or journals. Novartis shall have the right to review a draft of each publication and presentation (including, but not limited to, full manuscripts, abstracts, poster presentations and oral presentations) of results of the Study prior to its submission or disclosure to anyone not affiliated with Novartis or the Sponsor. A copy of each proposed publication and presentation shall be submitted to Novartis for review at least thirty (30) business days for manuscripts, and fifteen (15) business days for abstracts, posters and oral presentations prior to such submission or disclosure. If publication is in a language other than English, the Sponsor shall provide Novartis the abstract in English for Novartis' review prior to submission and/ or presentation. The Sponsor and the Principal Investigator acknowledge that such right is for the purpose of enabling Novartis to provide peer input regarding the scientific accuracy of data, verify that proprietary information is not being inadvertently divulged, to secure intellectual property rights (as needed), and to provide any

relevant supplementary information prior to submission to congress or journal. In no circumstances will the review be undertaken with the purpose of influencing or amending the reported outcomes and the authors' interpretation of data in the publication.

7.2 At the request of Novartis, any Novartis Information contained therein shall be excised from the proposed publication or presentation.

7.3 Novartis may require any proposed publication or presentation to be delayed for up to four (4) months to enable a patent application to be prepared and filed. The four (4) month period shall commence on the date of receipt of the proposed publication or presentation, or from the date when all relevant data from the Study are made available to Novartis, whichever is later.

7.4 Novartis' support must be disclosed in the acknowledgement section of the publication(s).

7.5 In addition, Sponsor shall share with Novartis a copy of the final publication upon presentation (abstract, poster, oral presentation) and/or a copy of the final journal manuscript.

8. USE OF THE SPONSOR'S OR NOVARTIS' NAME

The Sponsor, the Principal Investigator and Novartis will, and will cause their Subcontractors and agents to, obtain prior written permission from the relevant party before using the name, symbols and/or marks of the other party in any form of publicity in connection with the Study, according to Section 5. This shall not include documents or legally required disclosure by the Sponsor or Novartis that identifies the existence of the Agreement.

9. CONFIDENTIALITY

9.1 Novartis may disclose to the Sponsor certain confidential and proprietary information and materials relating to the Study Drug and the Sponsor may disclose to Novartis certain confidential and proprietary information relating to the Study for the purpose of facilitating, supporting and/or conducting such Study. All confidential and proprietary information exchanged by Novartis and the Sponsor shall constitute "**Information**."

9.2 In consideration of Novartis' and the Sponsor's disclosure of Information to each other, each recipient agrees that, during the term of this Agreement and for a period of five (5) years from the termination or expiry of this Agreement, it shall retain in confidence the Information belonging to the other, and will prevent disclosure of such Information to third parties. These restrictions shall not apply to Information which:

(a) May be communicated to the Sponsor's scientific and/or (institutional) review committee(s) under a similar, appropriate understanding of the confidential nature of the proprietary information supplied and under a similar obligation of confidentiality as set forth herein;

(b) Is required, but only to the extent necessary to be disclosed, to obtain informed consent from those patients or subjects who are eligible and choose to participate in the Study. Notwithstanding the foregoing, such Information will not be provided in response to unsolicited inquiries by telephone or to individuals who are interested in information about the Study, but not potential Study patients;

(c) At the time of disclosure is or thereafter becomes available to the public through no fault of the receiving party;

(d) As shown by written records, was known to, or was otherwise in the possession of the receiving party or its Affiliate prior to the receipt of such Information from the other party;

(e) As shown by written records, is obtained by the receiving party from a source other than the other party and other than one who would be breaching a commitment of confidentiality to that other party by disclosing the Information to the receiving party; or

(f) As shown by written records, is developed by or on behalf the receiving party or its Affiliates independently of any disclosure made hereunder.

9.3 The Sponsor and Novartis shall ensure that their employees, Subcontractors and agents and any other persons assisting in the conduct of the Study to whom Information is disclosed are informed of the obligations of confidentiality under this Agreement and are made subject to the same obligations of confidentiality as set out herein.

9.4 Notwithstanding anything else in this Section 9, each party shall be permitted to disclose the other party's Information if obliged to do so by the order of a court or applicable law or regulation, provided that the receiving party notifies the disclosing party of such obligation prior to said disclosure insofar as possible to enable the disclosing party to take reasonable actions to avoid or minimize the degree of such disclosure and such Information is disclosed only to the extent necessary.

9.5 Notwithstanding anything else in this Section 9, Novartis shall be allowed under conditions not less strict than the conditions set forth under this Agreement to disclose Information belonging to the Sponsor to Novartis' Affiliates for the purposes of improving the knowledge of the Study Drug within Novartis and its Affiliates.

9.6 Notwithstanding anything else in this Section 9, Novartis shall be allowed under conditions not less strict than the conditions set forth under this Agreement to disclose Information belonging to the Sponsor, including Study Data, to Novartis' licensor of any rights relating to the Study Drug.

9.7 Notwithstanding anything else in this Section 9, the Sponsor will not be bound by any obligations of confidentiality where maintaining confidentiality could prejudice patient safety or welfare, or where it is obliged by law to disclose information.

9.8 The obligations set forth in this Section 9 shall survive discontinuation or completion of the Study.

10. OWNERSHIP OF DATA

10.1 The Study Data and all copyrights therein shall be the property of the Sponsor, subject to the rights of Novartis as specified in Section 11.

10.2 The Sponsor shall ensure that the Study Data are kept in orderly, safe and secure storage in accordance with regulatory requirements for document retention following the local archiving regulations for such data.

10.3 The Sponsor shall grant Novartis access to all Study Data generated in the course of the Study at no additional cost. Novartis shall have the right to make copies of the Study Data. Notwithstanding any other provision of this Agreement, Novartis and its Affiliates and their licensees or sublicensees shall have the right to use the Study Data for all purposes,

including, but not limited to, regulatory purposes (including filing), patent purposes, and publication referencing purposes at no additional costs.

10.4 Sponsor shall ensure that patient informed consent identifies all anticipated purposes for use of Study Data and shall ensure patient informed consent permits the sharing of Study Data with Novartis, its Affiliates and any successors and assigns of either party, including those located outside the European Economic Area. In obtaining and documenting the patient informed consent, Sponsor shall comply with the applicable regulatory requirement(s) and laws, and shall adhere to ICH GCP and to the ethical principles as laid out in the Declaration of Helsinki.

11. INTELLECTUAL PROPERTY

11.1 Apart from any copyright in the Study Data any Invention, whether patentable or not, made by the Sponsor, its employees and agents and any other persons assisting with the conduct of the Study which relates to the Study Drug and any related Intellectual Property thereto shall be assigned to Novartis ("**Novartis Intellectual Property**").

11.2 Copyright in the Study Data and any Invention, whether patentable or not, made by the Sponsor, its employees and agents and any other persons assisting with the conduct of the Study arising from the performance of the Study other than an Invention constituting Novartis Intellectual Property pursuant to Section 11.1 above shall be the property of the Sponsor ("**Sponsor Intellectual Property**"). The Sponsor may agree to apportion ownership of the Sponsor Intellectual Property to Subcontractors and third parties at its discretion. The Sponsor shall grant to Novartis and its Affiliates a non-exclusive, perpetual, fully paid-up, royalty-free, worldwide license, with the right to sublicense, to use such Sponsor Intellectual Property for any purposes and an exclusive first option as well as a right of first refusal to an exclusive, world-wide license (with the right to grant sub-licenses) to exploit such Sponsor Intellectual Property.

11.3 Sponsor agrees to, and to cause its employees and collaborators and the Principal Investigator to, execute promptly all documents and take all such other action as may reasonably be requested by Novartis to permit Novartis to obtain the benefit of its rights under this Agreement.

11.4 Sponsor shall ensure that the Principal Investigator and the Sponsor's employees and collaborators involved in the Study will comply with its obligations under this Agreement.

12. STATUS OF THE PARTIES

12.1 Each party is acting hereunder as an independent contractor. No provision of this Agreement shall be deemed to constitute any party as the agent, employee, partner, joint venture, or legal representative of any other party for any purpose whatsoever. No party is granted any express or implied right or authority to assume, or to create, any obligation or responsibility, or to execute any agreements or to make any commitments verbally or in writing for or on behalf of, or in the name of, any other party in any manner or thing whatsoever without that other party's express written consent.

13. TERMINATION

13.1 This Agreement may be terminated by either party for any reason upon not less than thirty (30) days' written notice.

13.2 Either party may terminate this Agreement in the event that 1) the other party commits a material breach and fails to remedy such breach within thirty (30) days from the receipt of a

notice informing the breaching party of its failure to comply with its obligations under this Agreement or any of the Annexes, or 2) as per Section 3.9.

14. CONSEQUENCES OF TERMINATION

14.1 Upon termination of Novartis' involvement in this Agreement for whatever reason all Novartis Information shall be returned to Novartis, subject to any regulatory and ethical requirements.

14.2 Within thirty (30) days following termination or completion of the Study, all unused Study Drug provided by Novartis shall be returned to Novartis at Novartis' expense, subject to the provisions of Annex 4.

14.3 In case of termination by the Sponsor according to Section 13.1 or 13.2, the Sponsor will provide Novartis with access to all Study Data including computer data files as well as any relevant software and source codes to enable Novartis to retrieve and satisfactorily access all computerized data. For purposes of this clause, Personal Data is excluded from the obligation of disclosure. In addition, the Sponsor shall provide Novartis with an abbreviated TPSR or abbreviated final report. Furthermore, Sponsor shall submit the study-related publications based to Study Data obtained before termination to scientific congresses and/or journals and Novartis shall have the right to review the draft(s) in accordance to the section 7 of the Agreement. Finally, pursuant to the section 18 of the Agreement, termination by the Sponsor will not affect all the rights and obligations which are intended to survive termination of this Agreement.

14.4 Upon the effective date of termination according to Section 13.1, or 13.2 the Sponsor shall conduct an accounting, subject to verification and approval by Novartis. Within thirty (30) days after receipt of adequate documentation setting forth the results of such accounting, Novartis will make payment to the Sponsor (in no event exceeding the difference between the maximum amount specified in Section 4.1 and the total amount paid previously by Novartis to the Sponsor under or in connection with this Agreement) for:

(a) All Study activities properly rendered and costs properly incurred by the Sponsor according to the terms of this Agreement up to the effective date of termination and not yet paid for; and

(b) Reasonable non-cancelable commitments properly incurred by the Sponsor for the conduct of the Study prior to receipt of notice of termination.

14.5 Notwithstanding anything else in Section 14.4, in case of termination by Novartis due to Sponsor's material breach, Novartis shall owe no further payment to the Sponsor.

14.6 The Sponsor will refund to Novartis within thirty (30) days following the termination date any funds advanced to it but not expended or irrevocably committed by the Sponsor prior to the date of termination.

15. WARRANTIES

15.1 The Sponsor represents and warrants to Novartis that it is not a party to any agreement which would prevent it from fulfilling its obligations under this Agreement and that during the term of this Agreement the Sponsor will not enter into an agreement to undertake studies

which would in any way restrict its ability to undertake the Study or fulfill its obligations under this Agreement.

15.2 The Sponsor warrants and represents to Novartis that it has the full right and authority to enter into this agreement, and that it is not aware of any impediment which would inhibit its ability to perform the terms and conditions imposed on it by such agreement.

15.3 The Sponsor warrants and represents to Novartis that the Sponsor's policies applicable to the performance of the Study are consistent with the terms of this Agreement and Protocol.

15.4 For the purpose of transparency, and to ensure Novartis is providing adequate funding, Sponsor shall disclose to Novartis any other funding received from a third party to undertake the Study, and as the case may be, Sponsor shall disclose the amounts received from the other supporting party. Sponsor shall disclose this information to Novartis along with the request for support.

16. DISCLAIMER

NOVARTIS AND/OR ITS AFFILIATES PROVIDES ALL MATERIALS HEREUNDER [, INCLUDING STUDY DRUG].] "AS IS" AND THEY MAKE NO WARRANTY OF ANY KIND, EXPRESS OR IMPLIED, CONCERNING SUCH MATERIALS OR THEIR MERCHANTABILITY OR FITNESS THEREOF FOR ANY PURPOSE, INCLUDING BUT NOT LIMITED TO NONINFRINGEMENT OF ANY THIRD PARTY INTELLECTUAL PROPERTY RIGHTS. UNDER NO CIRCUMSTANCES SHALL NOVARTIS AND/OR ITS AFFILIATES BE LIABLE IN ANY MANNER FOR CONSEQUENTIAL, INCIDENTAL, SPECIAL, OR INDIRECT DAMAGES. Any advice furnished by Novartis and/or its Affiliates is given free of charge and Novartis and/or its Affiliates assumes no obligation or liability for the advice given or the results obtained and any such advice shall not constitute a warranty as to any matter, all such advice being given and accepted at the recipient's risk.

17. NOTICE

Any notice required or permitted hereinunder shall be in writing and shall be deemed given as of the date it is (A) delivered by hand or (B) sent by registered or certified mail, postage prepaid, return receipt request, and addressed to the party to receive such notice at the address set forth below, or such other address as is subsequently specified in writing:

If to Novartis: 18 Fl. Yonsei Jaedan Severance Bldg,84-11,Namdaemunro 5-ga Joong-gu, Seoul, Korea

Medical Matter: Minseok Park, MSL **Contract Matters: Minseok Park, MSL**
NAME

If to Sponsor:
Medical Matters: Prof. Yun-Sik Yang **Administrative Matters: Prof. Yun-Sik Yang**

18. SURVIVAL

Except where explicitly provided elsewhere herein, termination of this Agreement for any reason, or expiration of this Agreement, will not affect: (i) obligations, including the payment of any sums which have accrued as of the date of termination or expiration, and (ii) rights and obligations which, from the context thereof, are intended to survive termination or expiration of this Agreement.

19. ENTIRE AGREEMENT

This Agreement (together with any documents referred to herein) constitutes the entire and only agreement and understanding between the parties with respect to its subject matter and supersedes any previous agreements, understandings, or arrangements between the parties in respect of the Study (whether oral or written). Any claimed representation, promise or condition in connection with the subject matter of the Agreement that is not incorporated herein shall not be binding upon any party. No modification, extension, waiver, or other variance of any provision hereof, or any release of any right hereunder, shall be valid or binding unless the same is in writing and signed by all parties. In the event of any conflict between the operative provisions of this Agreement and the Annexes hereto, the operative provisions of this Agreement shall govern.

20. AMENDMENT

This Agreement and the Protocol may be extended, renewed or otherwise amended at any time by the mutual written consent of parties hereto.

21. FORCE MAJEURE

Neither the Sponsor nor Novartis shall incur any liability to any other party in the event of non-performance or delay in the performance of its obligations hereunder if caused directly or indirectly by strikes, lockouts, riots, sabotage, act of war or piracy, destruction of essential equipment by fire, explosion, storm, flood, earthquake, failure of power supplies or transport facilities, failure of agents, or sub-contractors or any other event or circumstances whatsoever beyond the reasonable control of the party liable to perform for a period equal to any such non-performance or delay. However, the party affected shall use all reasonable endeavours to limit the amount of non-performance or delay in performance of its obligations hereunder.

22. WAIVER

The failure of a party at any time to require full or partial performance of any provisions of this Agreement will not affect in any way the full right of that party to require that performance subsequently. Any waiver of a breach of this Agreement must be in writing signed by the party granting the waiver.

23. SEVERABILITY

Any provision of this Agreement which is declared void or unenforceable by any competent authority or court shall to the extent of invalidity or enforceability be deemed severable and not affect the provisions of this Agreement which shall continue unaffected.

24. ASSIGNMENT

Neither party may assign its rights and obligations under this Agreement without the other party's prior written consent, except that Novartis may (a) assign its rights and obligations under this Agreement or any part hereof to one or more of its Affiliates; or (b) assign this Agreement in its entirety to a successor to all or substantially all of its business or assets to which this Agreement relates. Any permitted assignee will assume all obligations of its assignor under this Agreement (or related to the assigned portion in case of a partial assignment). Any attempted assignment in contravention of the foregoing will be void. Subject to the terms of this Agreement, this Agreement will be binding upon and inure to the benefit of the parties and their respective successors and permitted assigns.

25. NO TRANSFER OF PROPRIETARY RIGHTS NOT SPECIFIED

It is agreed that neither Novartis nor the Sponsor transfers to the other by operation of this Agreement any patent right, copyright, or other proprietary right of either party, except as specifically set forth herein.

26. LIABILITY

Subject to the provisions of Section 28.2, the Sponsor as the Sponsor of the Study shall be liable for all damages incurred by a patient arising out of the performance of the Study.

27. INSURANCE

27.1 The Sponsor as the sponsor of the Study agrees to take out adequate clinical trial insurance or make alternative arrangements as is necessary and required by applicable regulatory requirements to cover its obligations as Sponsor of the Study including, but not limited to, providing full compensation (including indirect losses) to participants in the Study suffering injury or death or loss caused by the administration of drugs or any clinical intervention or procedure in accordance with the relevant Protocol and all legal requirements laid down by local regulations.

27.2 Upon Novartis' request the Sponsor shall provide evidence of such insurance or alternative arrangement.

28. INDEMNIFICATION

28.1 The Sponsor agrees to indemnify and hold harmless Novartis, its Affiliates and their respective employees, directors, officers, representatives, sub-contractors, and agents from and against any loss, damages, liabilities, reasonable costs and expenses (including reasonable attorney's fee and expenses), incurred in connection with any claim, proceeding, or investigation arising out of this Agreement and of this Study, except to the extent as provided under Section 28.2.

28.2 Novartis agrees to indemnify and hold harmless the Sponsor and its employees, directors, officers, representatives, sub-contractors and agents from and against any loss, damages, liabilities, reasonable costs and expenses (including reasonable attorney's fee and expenses) incurred in connection with any claim, proceeding, or investigation arising out of this Agreement (hereinafter referred to as "**Claims**") to the extent that such Claims arise from [(i)] the willful wrongful act or omission or the negligence of Novartis[; or (ii) a product liability issue regarding the Study Drug furnished to the Sponsor under this Agreement, provided the Study Drug has been used in accordance with the Protocol.

29. LAW AND JURISDICTION

This Agreement shall be governed by, and construed in accordance with, the substantive laws of Korea without regard to the conflict of law provisions thereof. For the purpose of any dispute which cannot be resolved amicably, the parties submit to the exclusive jurisdiction of the Seoul Central District Court.

IN WITNESS WHEREOF, the parties intending to be bound have caused this Agreement to be executed by their duly authorized representatives.

NOVARTIS KOREA LTD.

By: _____

Name: Haksun Moon

Title: CPO Head & Country President

Date: _____

Wonkwang University Hospital

By: _____

Name: Du Young Choi

Title: President & CEO

Date: _____

Acknowledged and agreed:

_____

[Principal Investigator, Prof. Yun-Sik Yang]

List of Attachments:

Annex 1:	**Final Signed Protocol for the Study (dated xxxxx)**
Annex 2:	**Key Contacts**
Annex 3:	**Payment Plan**
Annex 4:	**Drug Supply: Table of activities and responsibilities**
Annex 5:	**Safety data collection and reporting responsibilities**
Annex 6:	**Cover sheet for use when transferring safety information**
Annex 7:	**Signed Attestation Form**

ANNEX 1-FINAL NOVARTIS APPROVED PROTOCOL FOR THE STUDY

Investigator Initiated Trial

(1) Title of study

Effects of Ranibizumab to delay or regression non-proliferative diabetic retinopathy(NPDR) with DME assessed by microaneurysm changes: A pilot study

(2)Institution

Dept. of Ophthalmology, Wonkwang Univ. School of Medcine, Icksan Jeonbuk, South Korea

(3) Principal Investigator / Sub Investigator

Name : Yun-Sik Yang

Address : Dept. of Ophthalmology, Wonkwang Univ. School of Medcine

(4) Study Design

single center, prospective, interventional, one arm, pilot study

(5) Objectives

Objectives: To evaluate the effects of intravitreal Ranibizumab injection on microvascular changes in eyes of mild-to-moderate NPDR with DME.

Primary objective: To compare microvascular changes assessed by microaneurysm counts in eyes of mild-to-moderate NPDR with DME after intravitreal Ranibizumab injection from baseline through 6 months after treatment.

Secondary objectives: To investigate other efficacy endpoints including other microvascular, anatomical, visual acuity change and safety in mild-to-moderate NPDR with DME after intravitreal Ranibizumab injection from baseline through 6 months after treatment.

(6) Study rationale

Diabetic retinopathy is the leading disease that causes acquired vision loss after 20 by making diabetic macular edema and neovascularization. In recent young generation, as prevalence of type 2 diabetes is growing, the burden of sight-threatening retinopathy is increasing on trend.1

Pathologically, angiogenesis is a main cause that destroys the structure of the eye and induces the visual function disorder as VEGF playing an important role in increasing the migration and proliferation of endothelial cells and increasing the permeability of the blood vessels.2,3

VEGF is made from the endothelial cells of retinal tissue, perivascular cells, pigment endothelial cells by hypoxia. And hypoxic condition of intraocular tissues is a key regulator of intra ocular angiogenesis by VEGF, the balance between VEGF and angiogenesis inhibitors determines the neovascular proliferation in diabetic retinopathy.4

VEGF is also inducing the expression of cell-to-cell contact molecule (intracellular adhesion molecule-1, ICM-1) and the adhesion of leukocytes to help the inflammatory response5, as mediator which destroys the blood retinal barrier, affecting the protein of tight junctions, making a microaneurysm and increasing permeability of capillary, that makes the liquid leakage and macular edema.5,6

Microanuerysm is the earliest clinical manifestations, the saccular local lesion that perivascular cells protruding in

damaged areas on the capillary wall. According to Stitt AW et al9, diabetic microaneurysm is non-functioning extrusion of the vascular system from the deep part of inner retinal capillary plexus.

It is sometimes disappeared by being blocked with blood clots, on the other hand, new microanerysm is occurred in the other vascular bed structure.

Through these changes, we know the course of a diabetic retinopathy and it is known that the generation rate of microaneurysm is associated with the clinically significant progression of macular edema (CSME) in mild-to-moderate nonproliferative diabetic retinopathy .10,11

In addition, the number of microanerysm is an important prognostic indicator which can estimate the progression or regression of diabetic retinopathy, as predicting whether becoming better or worse in diabetic retinopathy.12

Kohner and Sleightholm13 describe this concept at first time in 1986, its association with the number of microvascular flow and the severity of diabetic retinopathy. In recent years it is reported that measuring the number of microaneurysm and the turnover rate associated with the appearance or disappearance of microaneurysm, are predictors in progression of diabetic retinopathy and macular edema.14

To delay the progression of diabetic retinopathy and to improve macular edema, the laser photocoagulation have been the important role.15 Although the laser photocoagulation have had treatment effect in the diabetic retinopathy by reducing the amount of VEGF in micraneurysm and by degenerating the neovascularization after laser therapy, there was a problem that has many limitations - peripheral visual field defects, night blindness, progression of macular edema etc., and that the disease does not cured in a good time because of limits of laser therapy due to cataract, vitreous hemorrhage and turbidity. As an alternative method to solve these limitations, there is an anti-VEGF therapy.6 According to a previous study result, intraocular injection of Bevacizumab inhibits occurring of neovascularization by blocking the VEGF receptor .17

Recently, several studies have been reported that when injected intravitreal anti-VEGF, macular edema is improved and neovascularization is inhibited, by reducing the leakage of neovascularization.3

Especially, Leicht SF et al18 reported the number of microaneurysms and turnover rate in NPDR(non-proliferative diabetic retinopathy) patients injected with Ranibizumab. And the result showed entire number of the microaneurysms and turnover rate are decreased, which could be mean the regression of diabetic retinopathy and it could decide the therapeutic effect.

On this study, through the fluorescein fundus angiography, the average number of microaneurysms was significantly decreased after intravitreal injection of anti-VEGF therapy ($p<0.05$). The decrease of 35.70±24.79% in the treatment group was statistically higher than 13.95±38.21% in the control group of the fellow eye ($p<0.05$).

The result is found because decreased concentration of intravitreal VEGF inhibits the progression of diabetic retinopathy, such as endothelial cell proliferation and endothelial cell damage on retinal capillary and perivascular cells.

Sjølie AK et al12 reported up-regulation of VEGF occuring microaneurysms causes endothelial cell proliferation and inflammation and effusion reaction, so anti-VEGF is effective in early diabetic retinopathy. But there is less effectiveness in late diabetic retinopathy as it reaches the non-changing point. Also Kohner EM et al19 reported diabetic retinopathy lesions are reversible and could be delayed in early diabetic retinopathy.

So far, changes of microaneurysms in late diabetic retinopathy is uncertain, and if there would be a finding according to anti-VEGF therapy, we could get a clue of surrogate marker which represents treatment results in diabetic retinopathy.

This study was designed to find the clinical evaluation and reduction rate through fluorescein angiography as microaneurysm examination tools to research NPDR with DME treatment results assessed by microaneurysm counts, timely monitored with anti-VEGF therapy.

(7) Number of centers & patients, inclusion/exclusion criteria

-25 patients, 1 center

- Inclusion criteria

  - Patients (Male & female) > 40 years of age

- Type 2
- Best corrected visual acuity > 20/200 (Snellen equivalent using Early Treatment Diabetic Retinopathy Study chart)
- Central retinal thickness of > 300 um on optical coherence tomography
- Nonproliferative diabetic retinopathy (NPDR) with diabetic macular edema

- Exclusion criteria

- PDR – NVE & NVD
  - Early PDR – New vessels ; and criteria not met for high-risk PDR
  - High risk PDR – New vessels on or within one disc diameter of the optic disc (neovascularization of the disc) > standard photograph 10A with or without vitreous or preretinal hemorrhage ; or vitreous and/or preretinal hemorrhage accompanied by new vessels, either NVD < standard photograph 10A or new vessels elsewhere (NVE) > 1/4 disc area
- Vitreous hemorrhage
- Prior intraocular operation history.
  - Pars Plana Vitrectomy, RD surgery, recent (4 months) cataract Op, et al
- Prior any intravitreal injection history.
  - Lucentis, Eylea, Macugen, Avastin, Triamcinolone et al
- Prior pan retinal photocoagulation(PRP) or sector scatter photocoagulation was done.
- Uncontrolled hypertension.
- Uncontrolled glaucoma.

(8) Pharmacovigilance

AE/SAE/Pregnancy will be collected as below;

- **Adverse event reporting:** An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug.

- Serious adverse event reporting

  An SAE is defined as an event which is fatal or life-threatening or results in persistent or significant disability/incapacity or constitutes a congenital anomaly/birth defect or requires inpatient hospitalization or prolongation of existing hospitalization or medically significant

  * Any other protocol specific SAE criteria or SAE exemption will be described on protocol.

  Every SAE, regardless of suspected causality, occurring after the patient signs the informed consent must be reported to Novartis after learning of its occurrence. All SAE form should be reported to local Novartis Safety Desk according to agreed procedure with Novartis within 15 days of learning by the investigator.

- **Pregnancies:** Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the sponsor, and the sponsor should forward that form to the local Novartis Safety Desk according to agreed procedure with Novartis within 15 days of learning by the investigator.

(9) Study duration

Until 30 Jul 2017(CSR submission)

(10) Methodology

Primary and secondary endpoints:

Primary endpoint:

To compare other visual acuity, anatomical changes after intravitreal Ranibizumab injection from baseline through 6 months after treatment.

i) The changes in best corrected visual acuity (BCVA) using ETDRS chart. ii) The central macular thickness - Circle Diameters : 1 mm ETDRS by spectralis OCT ; Heidelberg Engineering.

Secondary endpoints:

To compare microaneurysmal changes and perifoveal non-perfusion area and safty after intravitreal Ranibizumab injection from baseline through 6 months after treatment.

i) The total number of microaneurysm by fundus photo using Retmarker DR(version 1.0.2) software.

ii) The microaneurysm formation rate : Number of new MAs detected/month. iii) The microaneurysm disappearance rate : Number of MAs that resolved/month. iv)The microaneurysm turnover. v) Perifoveal non-perfusion area in FAG (mm^2) using ImageJ software (version 1.52a) by FAG image.

vi) Safety parameters : Systemic adverse events (MI, CVA, etc), Ocular adverse events (retinal detachment, RPE tear, endophthalmitis, uveitis, vitreous hemorrhage, subretinal hemorrhage, cataract , IOP elevation, etc).

single center, prospective, interventional, one arm, pilot study

Evaluation Participants will be evaluated with a full ocular examination at each visit (VA measurement, tonometry, slit lamp exam). Fluorescein angiography (FA) will be performed at baseline, at 3 months after baseline and at the last visit(6 months after baseline), and OCT will be performed monthly (baseline and 1, 2, 3, 4, 5, 6 months from baseline).

The MAs and perifoveal non-perfused areas in individual retinas were evaluated at 6 months using fundus photography and FA imaging. The Retmarker (version 1.0.2 by Retmarker Ltd, Coimbra, Portugal) software was used for automatic measurement and analysis of changes in number and extent of MAs on fundus photographs and to calculate the total number and turnover of MAs.

Perifoveal non-perfused area was estimated using the early FA image (from each of the three examinations) in which both the vascular arch and the non-perfused area were clearly visualized. Subsequently, the ImageJ software (version 1.25a 23/04/2018 by ImageJ, USA) was used for scaling each image to 200 μm and for equalizing the contrast and sensitivity of each picture to the maximum possible extent, by auto-adjustment of brightness and contrast. The raw red-green-blue (RGB) images were then converted to 8-bit images, with the threshold set for optimal visualization of the non-perfused area. The same threshold was applied to all images of the same patient.

Statistical Analysis Plan

Result analysis The investigators compare the differences between at baseline, at 3 month, and at 6 month. Statistical analyses will be performed using SPSS ver.18.0 (SPSS Inc., Chicago, Il, USA). Kolmogorov-Smirnov test was applied to test for normality of sample group data. The repeated measures analysis of variance with Bonferroni correction was used to analyze continuous outcome measures, including BCVA, CRT, total number of MAs, MA formation rate, MA disappearance rate, MA turnover, and perifoveal non-perfused area, before and after completion of 6 months of IVR therapy. A P-value <0.05 was considered statistically significant.

Table 1. Schedule of visits and procedures

Note: X = procedure to be performed, R = rescue treatment	Baseline Month 0 (Visit 1)	Month 1 (Visit 2)	Month 2 (Visit 3)	Month 3 (Visit 4)	Month 4 (Visit 5)	Month 5 (Visit 6)	Month 6 (Visit 7)
Informed consent	X						
Review eligibility criteria	X						
Demographics	X						
ETDRS BCVA	X	X	X	X	X	X	X
Slit lamp exam	X	X	X	X	X	X	X
IOP	X	X	X	X	X	X	X
OCT	X	X	X	X	X	X	X
Color Fundus Photo	X	X	X	X	X	X	X
FA	X			X			X
ICGA	X			X			X
Lucentis® injection	X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X

(11) Statistics

We compare the differences between at baseline, at 3 month, and at 6 month. Statistical analyses will be performed using SPSS ver.12.0 (SPSS Inc., Chicago, Il, USA). The Wilcoxon signed rank test will be examined for timely changes in microvascular change (microaneurysm, non-perfusion area, cotton wool spot & hard exudate)

(12) references

1) Kim HK, Oh TS, Lee SM, Lee JB. The initial fundus examination and severity of diabetic retinopathy at a primary eye clinic. J Korean Ophthalmol Soc 2005;46:982-8.

2) Liinamaa MJ, Savolainen MJ. High vitreous concentration of vascular endothelial growth factor in diabetic patients with proliferative retinopathy using statins. Ann Med 2008;40:209-14.

3) Funatsu H, Yamashita H, Noma H, et al. Aqueous humor levels of cytokines are related to vitreous levels and progression of diabetic retinopathy in diabetic patients. Graefes Arch ClinExpOphthalmol 2005 Jan;243:3-8. Epub 2004 Jul 17.

4) Crawford TN, Alfaro DV 3rd, Kerrison JB, Jablon EP. Diabetic retinopathy and angiogenesis. Curr Diabetes Rev 2009 Feb;5:8-13.

5) Ishida S, Usui T, Yamashiro K. VEGF164 is pro inflammatory in the diabetic retina. Invest Ophthalmol Vis Sci 2003;44:2155-62.

6) Hoeben A1, Landuyt B, Highley MS, et al. Vascular endothelial growth factor and angiogenesis. Pharmacol Rev 2004 Dec;56:549-80

7) Roy S, HaJ, Trudeau K, Beglova E. Vascular basement membrane thickening in diabetic retinopathy. Curr Eye Res 35:1045-56.

8) Hammes HP. Pericytes and the pathogenesis of diabetic retinopathy. Horm Metab Res 2005 Apr;37 Suppl 1:39-43.

9) Stitt AW, Gardiner TA, Archer DB. Histological and ultrastructural investigation of retinal microaneurysm development in diabetic patients. Br J Ophthalmol 1995;79:362-67.

10) Ribeiro ML, Nunes SG, Cunha-Vaz JG. Microaneurysm turnover at the macula predicts risk of development of clinically significant macular edema in persons with mild nonproliferative diabetic retinopathy. Diabetes Care 2013;36:1254-59.

11) Haritoglou C, Kernt M, Neubauer A, et al. Microaneurysm formation rate as a predictive marker for progression to clinically significant macular edema in nonproliferative diabetic retinopathy. Retina 2014 Jan;34:157-64.

12) Sjølie AK, Klein R, Porta M, et al. Retinal microaneurysm count predicts progression and regression of diabetic retinopathy. Post-hoc results from the DIRECT Programme. Diabet Med 2011;28:345-51.

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15) Diabetic Retinopathy Study Research Group. Photocoagulation treatment of proliferative diabetic retinopathy : clinical application of Diabetic Retinopathy Study(DRS) : DRS report No. 8.

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16) Ferrara N, Hillan KJ, Gerber HP, Novotny W. Discovery and development of bevacizumab, an anti-VEGF antibody for treating cancer. Nat Rev Drug Discov 2004;3:391-400.

17) Han XX, Guo CM, Li Y, Hui YN. Effects of bevacizumab on the neovascular membrane of proliferative diabetic retinopathy: reduction of endothelial cells and expression of VEGF and HIF-1 α . Mol Vis 2012;18-19.

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19) Kohner EM, Stratton IM, Aldington SJ et al. Microaneurysms in the development of diabetic retinopathy(UKPDS42). UK Prospective Diabetes Study Group. Diabetologia 1999;42:1107-1112.

20) Horii T, Murakami T, Nishijima K, et al. Optical coherence tomographic characteristics of microaneuryms in diabetic retinopathy. Am J Ophthalmol 2010;150:840-48.

ANNEX 2-KEY CONTACTS

1) Novartis Safety contacts shall be: safety.kor@novartis.com, Tel: 02-768-9007 Fax: 02-780-8487

2) Novartis Medical contact shall be: minseok.park@novartis.com / 02-768-9125

3) Sponsor key contact shall be: ysyang@wku.ac.kr / 063-859-1382

ANNEX 3- PAYMENT PLAN

The agreed Study budget for the clinical trial is a maximum amount of *(79,063,000 KRW (VAT excluded))*

The payments will be due and transferred to the Sponsor in accordance the following milestones:

1. 10%(maximum) for study start up activities
   a. (max of 5%) upon Agreement execution and Novartis approval of protocol
   b. (rest of the initial 10%) upon IRB/EC/HA final approved protocol & FPFV
2. 30% of total agreement at 10% recruitment
3. 20% of total agreement at 50% recruitment
4. 20% of total agreement at 100% recruitment
5. 10% of total contract at provision of the final study report (TPSR)
6. 10% of the total contract at receipt by Novartis of the final publication or confirmation of publication submission (including but not limited to: congress abstracts, posters, oral presentation or journal publication, hereinafter the same).

   However, if the final publication or confirmation of publication submission is provided between twenty-four (24) and thirty-six (36) months from LPLV, only 5% of total contract will be paid. If the final publication or confirmation of publication submission is not provided within thirty-six (36) months from LPLV, the Sponsor shall pay to Novartis 10% of total contract as a penalty.

ANNEX 4- DRUG SUPPLY ACTIVITIES/ RESPONSIBILITIES

Prior to any Study Drug shipment, the Sponsor shall provide Novartis with the public registration number of the Study. Provided the Sponsor has given Novartis the study number which is registered with the health authorities and a copy of the approvals from the appropriate health authorities and ethics committees, Novartis shall supply the Sponsor with sufficient supplies of the Study Drug to conduct the entire Study.

Novartis shall bear the costs arising from the shipment of the Study Drug to the Participating Sites, including customs duties or VAT if applicable.

The Sponsor shall observe the standard requirements of Good Manufacturing Practices (GMP) for Investigational Medicinal Products.

The Sponsor will maintain records of the packaging and labeling (if applicable), receipt, storage, administration or dispensing, return and destruction of Study Drug, identifying (but not necessarily by name) each patient to whom the drug is administered or dispensed, and will make these records available to Novartis at any time with the patient details redacted so as to preserve the patients' anonymity. The Sponsor is responsible for labeling according to local laws and regulations. The Sponsor shall ensure that any shipment of Study Drug is inspected upon receipt. The Sponsor shall ensure that any notice of defect or non-conformity is sent to Novartis within ten (10) days from receipt of Study Drug. The failure to provide such notice shall be deemed an acceptance of Study Drug by the Sponsor or its Subcontractors. Latent defects which are detected later shall be immediately reported to Novartis for further processing within Novartis. Shipment of Study Drug may be withheld at any time for failure to promptly respond to requests for production of the Study Drug records. Upon completion or termination of the Study, the Sponsor shall follow Novartis' instructions regarding the return or disposal of all unused Study Drug. The Sponsor shall be responsible for compliance with all laws and regulations applicable to any destruction or disposal of Study Drug at Participating Sites. The Sponsor will follow the instructions of Novartis in case Novartis determines that a recall of the Study Drug is required and in addition, the Sponsor will inform Novartis should the Sponsor determine that a recall of the Study Drug is required.

The Sponsor will keep all Study Drug under appropriate storage conditions and in a secured area accessible only to authorised personnel. Exceptions to storage conditions should be reported to Novartis.

Without limiting the generality of the foregoing, Novartis may perform drug supply activities on behalf of the Sponsor as set forth in the table below:

[Please choose between option A or B; option B is applicable for open label studies]

		IIT Trials								
CATE-GORY	Activity/Responsibilities	Option A Supply of blinded Patient Packs by NVS (full support)				Option B Supply of Bulk/Primary packaged unlabeled Drug product by NVS				
		TRD	CPO	NVS QPs	Sponsor	TRD	CPO	NVS QPs	SupplyCRO *	Sponsor
IMP SUPPLY PROVISION of bulk DP	Supply of bulk IMPs (*fill-in, examples below*): Active Placebo Comparator Novartis Marketed Product (provided by CPO)	N/A	N/A	N/A	N/A	 X X X	 X X			
	TRD QA Release of Drug Product (CofA)	X				X for TRD supplied DP				
IMP PACKAGING	Label design	X	X						X	X
	Provide information for labels (e.g., storage conditions)	X				X				
	IMP Label approval				X					X
	IMP Packaging and Labeling	X							X	
	Technical Release of final packaged IMP (CoC)	X						X	X	
IMP CERTIFICATION	QA Agreement between:			X	X			X	X	
	QP Batch certification of bulk/primary packed IMPs Step 1: Manufacturer applies GMPs equivalent to EU GMPs Step 2: Compliance with Product Specification File for bulk IMP (CoA level) Step 3: Compliance with approved Quality Part of IMPD for bulk IMPs (CoA level), per EU country			X				X		

* Assumption: CRO is located in EU, participating countries are EU Member States. If this is not the case, additional import requirements may have to be taken into account.

		IIT Trials								
CATE-GORY	Activity/Responsibilities	Option A Supply of blinded Patient Packs by NVS (full support)				Option B Supply of Bulk/Primary packaged unlabeled Drug product by NVS				
		TRD	CPO	NVS QPs	Sponsor	TRD	CPO	NVS QPs	SupplyCRO	Sponsor
IMP CERTIFICATION	QP Batch certification of packed IMP Step 1: Manufacturer applies GMPs equivalent to EU GMPs Step 2: Compliance with Product Specification File for packed IMP (CoC level) Step 3: Compliance with approved Quality Part of IMPD for packed IMPs (CoC level), per EU country			X					CRO QP	
	Sponsor release for shipment to trial site per EU country (elements mentioned below, documentation in trial file): CTA Approval per EU country EC Approval per EU country QP Batch certification of packed IMPs				X					X
DISTRIBUTION	Procurement of Import licenses, as appropriate		X						X	
	Storage and distribution of patient packs to trial sites via country depots		X						X	
	Return and Destruction of trial medication		X						X	
	Recalls	X	X	X	X	X	X	X	X	X
	Complaints	X	X	X	X	X	X	X	X	X

		IIT Trials								
CATE-GORY	Activity/Responsibilities	Option A Supply of blinded Patient Packs by NVS (full support)				Option B Supply of Bulk/Primary packaged unlabeled Drug product by NVS				
		TRD	DRA	NVS QPs	Sponsor	TRD	DRA	NVS QPs	Supply CRO	Sponsor
CTA ACTIVITIES	Get EUDRACT number and inform involved parties (Sponsor: report to Clinical Liaison)				X					X
	(1) Provide Novartis (cross)-referencing letter and SmPC, as applicable		HQ or CPO				HQ or CPO			
	Provide QP Declaration for manufacturers in 3rd countries to Global DRA (HQ), as applicable			X				X	CRO QP	
	Provide Manufacturing Authorisations (EU Drug product manufacturing sites only) to Global DRA (restricted to sites used/involved by Novartis)	Reg CMC				Reg CMC			X	
	Provide other quality-related documents to Global DRA, as applicable (e.g., TSE certificate)	Reg CMC				Reg CMC			X	
	Provide IMPD Quality section to Global DRA, as applicable	Reg CMC				Reg CMC			X	
	Ensure publishing of the IMPD in REDI and Dispatch the Quality dossier (IMPD) and Novartis Cross-reference letter via REDI to DRA CPOs, as applicable		Gl. DRA (HQ)				Gl. DRA (HQ)			
	Submit IMPD Quality section to HA, referring to Sponsor's EUDRACT No., if applicable		CPO				CPO			
	Inform Sponsor QP and Global DRA about submission of IMPD Quality section, as applicable		CPO				CPO			
	Inform QPs about CTA approval (including amendments) and any relevant updates that				X (via Clinical					X (via Clinical

CATE-GORY	Activity/Responsibilities	IIT Trials								
		Option A Supply of blinded Patient Packs by NVS (full support)				Option B Supply of Bulk/Primary packaged unlabeled Drug product by NVS				
		TRD	DRA	NVS QPs	Sponsor	TRD	DRA	NVS QPs	Supply CRO	Sponsor
	happened during HA review (for IIT: Global DRA/REG CMC /DRA CPO also to be informed via Clinical Liaison)				Liaison)					Liaison)
	Provide IMPD Quality section to QP or delegate, as applicable		CPO				CPO			
	Provide substantial amendment IMPD Quality documentation to Global DRA, as applicable	Reg CMC				Reg CMC				
	Ensure REDI publishing of the substantial amendment IMPD documentation and Dispatch the amended Quality dossier via REDI to DRA CPO, as applicable		GlDRA				GlDRA			
	Submit substantial amendments to IMPD Quality section to HA, as applicable		CPO				CPO			

(1) Novartis Cross-reference letter is provided by Global DRA for global study or DRA CPO for local study

CATE-GORY	Activity/ Responsibilities	IIT Trials								
		Option A Supply of blinded Patient Packs by NVS (full support)				Option B Supply of Bulk/Primary packaged unlabeled Drug product by NVS				
		TRD	DRA	NVS QPs	Sponsor	TRD	DRA	NVS QPs	Supply CRO	Sponsor

CONTRACTS	Sponsor – CRO for IIT Trials for Option B	Not applicable				X	X
	Novartis QP – CRO QP for Option B	Not applicable			X	X	

ABBREVIATIONS

CoA	Certificate of Analysis	HQ	Head Quarters
CoC	Certificate of Compliance	IMP	Investigational Medicinal Product
CPO	Country Pharma Organization	IMPD	Investigational Medicinal Product Dossier
CPO-QP	CPO Qualified Person	NVS	Novartis
CTA	Clinical Trial Authorization	QA	Quality Assurance
EC	Ethic Committee	QP	Qualified Person
EU	European Union	Reg-CMC	Global Regulatory-Chemistry, Manufacturing and Control
DRA	Drug Regulatory Affairs	SmPC	Summary of Product Characteristics
GMP	Good Manufacture Practice	TRD	Technical Research and Development
HA	Health Authority	TSE	Transmissible Spongiform Encephalopathy

For more information refer to the Novartis European Union Clinical Trial Directive 2001/20/EC/Investigator Initiated Trials Website educational material

http://www.novartisclinicaltrials.com/EUDirectiveIIT/landing.do

ANNEX 5- SAFETY DATA COLLECTION AND REPORTING RESPONSIBILITIES

1. SPONSOR'S RESPONSIBILITIES

1.1 The Sponsor shall be responsible for ensuring that adverse events and other relevant safety information are recorded as specified in the Protocol and appropriately reported to the relevant health authorities, ethics committees and Study investigators according to Applicable Laws in the countries where the Study is conducted.

1.2 The Sponsor shall forward to Novartis any SAEs, reports of drug exposure during pregnancy and reports of Study Drug misuse or abuse, including initial and follow up reports, arising from the Study in subjects exposed to the Study Drug, as soon as it becomes available, but in any event within fifteen (15) calendar days of becoming aware of such information, by transmitting it to Novartis at the contact information provided below in Section 1.9.

1.3 The Sponsor shall forward to Novartis any findings that might alter the current benefit-risk profile of the Study Drug or that would be sufficient to consider changes in the Study Drug's administration or in the overall conduct of the Study, as soon as it becomes available, but in any event within five (5) calendar days of becoming aware of such information, by transmitting it to Novartis at the contact information provided in Section 1.9.

1.4 The Sponsor shall report any other relevant/ important safety information to Novartis in the final study report and at such other periods as Novartis may request.

1.5 The Sponsor shall prepare and issue expedited safety reports for suspected unexpected SAEs ("SUSARs") in the Study in accordance with the applicable laws and regulations, this includes preparing and issuing Investigator Notifications (INs) or biannual SUSAR listings, where applicable by regulations. The Sponsor shall provide a copy of any Sponsor-generated INs to Novartis DS&E within fifteen (15) calendar days of first notification of the SUSAR or subsequent follow-up information, if IN is issued by investigator.

1.6 For each SAE report, report of Study Drug misuse or abuse and report of drug exposure during pregnancy arising from subjects exposed to the Study Drug] *OR* [For any Adverse Drug Reactions to Novartis products] *[Select the applicable option according to Section 1.3]* (both initial and follow-up reports), the Sponsor shall forward a Novartis IIT SAE reporting Form completed with full information (as known at the time of forwarding). The Sponsor shall ensure that at a minimum the form contains:

(a) Information on the person who contacted Sponsor (i.e., the initial reporter);

(b) Information about the patient or clinical trial subject;

(c) Details of the suspected Study Drug *[if study will involve a Novartis drug] OR* Details of the Novartis product(s) *[if study will not involve a Novartis drug] [Select the applicable option according to Section 1.3]*

(d) Details on the safety events experienced by the patient

1.7 The Sponsor shall send [all SAE reports, reports of Study Drug misuse or abuse and reports of drug exposure during pregnancy] OR [any Adverse Drug Reactions to Novartis products] *[Select the applicable option according to Section 1.3]* or other relevant safety information using the cover sheet attached in Annex 6.

1.8 The Sponsor shall send [all SAE reports, reports of Study Drug misuse or abuse and reports of drug exposure during pregnancy] OR [any Adverse Drug Reactions to Novartis products] [Select the applicable option according to Section 1.3] or other relevant safety information to:

Novartis DS&E contact information for forwarding individual safety reports

[Initial and follow-up reports shall be sent to local Novartis DS&E in the country (CPO) where the adverse event occurred. Any deviation from this standard workflow i.e. direct reporting to central DS&E processing site must be discussed and agreed with Clinical Trial Safety Operations (CTSO) at the Novartis Central DS&E Processing Site prior to the Agreement being signed. Depending on the route selected the appropriate option below must be selected]

Contact details	Who	Address	Fax
Local Novartis DS&E Department	*Safety.kor@novartis.com*	Novartis Korea Ltd., 18Fl, Yonsei Severance B/D, 10 Tongil-ro, Joong-gu, Seoul, 04527, Korea	02-780-8487

1.9 The Sponsor shall cooperate with all reasonable requests by Novartis to ensure that individual safety reports are sufficiently investigated, including requests to seek additional information relating to an individual safety reports or other relevant safety information.

1.10 The Sponsor shall perform AE reconciliation between the Sponsor's Study database and an output of the Novartis Safety Database at the following time points [*the below time points must not be updated to be less frequent, they may be updated to be more frequent*]:

- One year after First Patient First Visit and yearly thereafter *(delete if the study is expected to be completed within one year)*
- At Last Patient Last Visit

Note: When the Novartis product is in a pre- or peri- approval phase, when there are specific safety concerns under active investigation (e.g. recent report of fatal hepatic failure) or when the overall safety dataset warrants a more frequent reconciliation this will have been determined by the Medical Review Committee during the study concept approval and the above text must be adapted accordingly to reflect the decision.

The Sponsor will confirm that, for the period being reconciled, all information in the Sponsor's Study database that needed to be transferred to Novartis as per this Annex, are contained in the output from the Novartis Safety Database. Where discrepancies are identified the Sponsor shall send/resend the information to Novartis DS&E as per the contact information in Section 1.9 and using the cover sheet attached in Annex 6.

The Sponsor shall provide the Novartis Medical contact listed in Annex 2 with a written confirmation that the reconciliation was performed, the outcome of the reconciliation and documentation that, where discrepancies were identified, Novartis DS&E was informed (e.g. delivery confirmations).

The Sponsor shall prepare and submit all reports for the Study (e.g. Development Safety Update Report (DSUR), US IND Annual Report) to the applicable health authorities and ethics committees in accordance with Applicable Laws and shall provide a copy of each such report to the Novartis Medical contact listed in Annex 2 within one (1) month of such submission if applicable.

1.11 The Sponsor agrees that Novartis can make changes to these procedures as may be necessary or appropriate to comply with changes in applicable law or regulations relating to pharmacovigilance and safety data reporting. Any such changes shall be notified by Novartis to the Sponsor and this Annex shall be amended accordingly. Without prejudice to the foregoing, Sponsor shall amend its policies and procedures to enable Novartis to comply with applicable laws and regulations for the reporting of AEs and other relevant safety information.

2. NOVARTIS' RESPONSIBILITIES

2.1 Novartis shall be responsible for submitting the safety information received from the Sponsor, to the relevant health authorities globally, as applicable, in each country where Novartis has a marketing authorization or clinical trial authorization (CTA) for the Study Drug.

2.2 Novartis shall provide the Sponsor with a copy of any relevant Novartis-generated Aggregate Finding Safety Reports (AFSR) and Urgent Safety Measures (USM) related communications no later than fifteen (15) calendar days after the decision was made to prepare an AFSR or to implement an USM action plan.

2.3 Novartis shall prepare and issue INs for the Study Drug in accordance with Novartis' internal procedures. Novartis shall provide the Sponsor with a copy of Novartis generated INs for the Study Drug within fifteen (15) calendar days of first notification of the suspected unexpected SAE or subsequent follow-up information.

2.4 Novartis shall provide the Sponsor at the time points listed below, for the purposes of reconciliation, with an output from the Novartis Safety Database containing all safety reports received from the Sponsor for that study during the period being reconciled, [*the below time points must not be updated to be less frequent, they may be updated to be more frequent. To be aligned with Section 1.11*]:

- One year after First Patient First Visit and yearly thereafter *(delete if the study is expected to be completed within one year)*
- At Last Patient Last Visit

Novartis shall incorporate a summary of the Sponsor-generated DSUR for the Study into the Novartis DSUR for the Study Drug, if applicable.

ANNEX 6- COVER SHEET FOR USE WHEN TRANSFERRING SAFETY INFORMATION

This attached Cover Sheet must be submitted together with any individual safety cases to Novartis.

[CRFB002AKR15T / Efficacy of fixed monthly dosing of Ranibizumab (Lucentis®) on subretinal fluid associated with persistent retinal pigment epithelial detachment in neovascular age-related macular degeneration]

ANNEX 6.COVER
SHEET FOR USE WHE

ANNEX 7- ATTESTATION FORM

(Please insert the signed pdf of the Attestation Form)