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RANIBIZUMAB: A NOVEL THERAPEUTIC AGENT

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Abstract: -

Your study on the efficacy of laser combination therapy versus Ranibizumab monotherapy for anti-VEGF-resistant diabetic macular edema (DME) presents some important findings. Here's a concise summary of the key points:

To evaluate the effectiveness of laser combination therapy alongside anti-VEGF compared to Ranibizumab monotherapy in patients resistant to anti-VEGF treatment for DME.Best- Corrected Visual Acuity (BCVA): There was no significant improvement in BCVA between the two groups (laser combination therapy: +3.2 letters; Ranibizumab monotherapy: -7.5 letters; p = 0.165).BCVA Over Time: No significant change from visit 1 to visit 7 in either group (laser combination: 64.3 to 70.3 letters, p = 0.537; Ranibizumab monotherapy: 72.3 to 64.8 letters, p = 0.554).Central Foveal Retinal Thickness: Both groups showed no significant changes (laser combination: +9.3%; Ranibizumab monotherapy: -7.3%; p = 0.926)Intravitreal Therapy Sessions: No significant difference in the number of Ranibizumab injections (laser combination: 5.2; monotherapy: 6.0; p = 0.237). Laser combination therapy did not demonstrate superior effectiveness over Ranibizumab monotherapy for patients with anti- VEGF-resistant DME. The study suggests considering alternative treatments for these patients.

Key Words: Age-related macular degeneration, choroidal neovascular membrane, Lucentis [tm] [ranibizumab injection], vascular endothelial growth factor

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INTRODUCTION:

Diabetic macular Edema (DME) is a major cause of vision loss in patients with diabetic retinopathy. The pathogenesis of DME is closely linked to vascular endothelial growth factor (VEGF), which increases vascular permeability and leads to the accumulation of exudative fluid in the macula. Various treatment options are available for DME, including:

- Intravitreal injections of anti-VEGF drugs
- Focal laser photocoagulation
- Steroid injections

Vitrectomy Anti-VEGF Therapy

Anti-VEGF therapy has emerged as the first-line treatment for DME due to its demonstrated superiority in both functional and anatomical improvement. Ranibizumab, an anti-VEGF agent, is approved globally for treating DME. Numerous randomized clinical trials (RCTs)— such as RESTORE, RETAIN, RESOLVE, and RISE and RIDE—have established the therapeutic efficacy of Ranibizumab. These studies have shown that monotherapy with Ranibizumab can improve best-corrected visual acuity (BCVA) by approximately 7 to 12 letters from baseline after 12 weeks of treatment. This structure highlights the key information about DME, its association with VEGF, and the effectiveness of Ranibizumab in a concise manner.

Focal laser photocoagulation has historically been a first-line treatment for diabetic macular Edema. The Early Treatment of Diabetic Retinopathy Study (ETDRS) demonstrated that this method reduced the risk of moderate visual loss by approximately 50%. However, with the advent of anti-VEGF therapies, laser treatment has been relegated from its primary position.

In the BOLT study, focal laser photocoagulation was shown to decrease best-corrected visual acuity (BCVA) by about five letters from baseline after 12 weeks. In contrast, the anti-VEGF agent Bevacizumab improved BCVA by approximately five letters during the same period.

Combination Therapy

While combination therapy involving anti-VEGF agents and laser photocoagulation has proven effective, it is not classified as a first-line treatment. The RESTORE study indicated that combination therapy was equivalent to anti-VEGF monotherapy and significantly more effective than laser monotherapy, with improvements of +7.1, +7.9, and +2.3 letters from baseline after 12 months, respectively.

Furthermore, the RESTORE extension study found that prompt laser combination therapy yielded similar results to deferred laser combination therapy but was less effective than anti- VEGF monotherapy, with improvements of +6.7, +6.0, and +8.0 letters from baseline after 36 months, respectively. While many patients benefit from standard treatments like anti-VEGF therapy, a significant portion—approximately 18% to 30%—of DME cases show resistance to these agents, resulting in little to no therapeutic effect. This highlights the critical need for alternative treatment options for anti-VEGF-resistant DME.

To address this issue, we conducted a prospective study assessing the efficacy of combining anti-VEGF therapy with focal laser photocoagulation in patients resistant to anti-VEGF treatment. Specifically, the RELAND study included patients who were refractory to three months of initial anti-VEGF therapy for naïve DME. The primary objective of this study was to determine whether this combination therapy could provide effective management without the need for ongoing anti-VEGF treatment in patients identified as resistant.

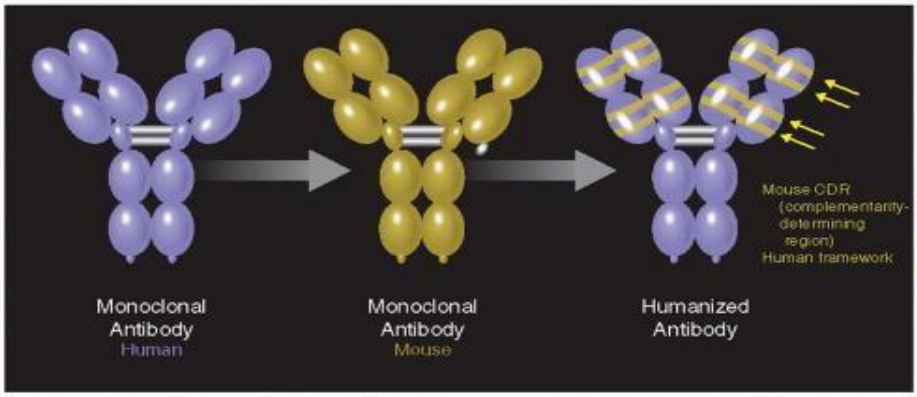

Fig-1.

MATERIALS AND METHODS:

Here's a concise summary of the RELAND study that captures the essential details while enhancing clarity:
RELAND Study Overview
The RELAND study (jRCTs061180035, UMIN000024208) was a multicentre, prospective, exploratory trial conducted across 11 clinical sites in Japan, including:
Kyusyu University Hospital

- UBE Kohsan Central Hospital
- Ogori Daiichi General Hospital
- Shimonoseki Medical Centre
- Shuto General Hospital
- Tokuyama Central Hospital
- Nagato General Hospital
- Fujimoto Eye Clinic
- Yamaguchi Red Cross Hospital
- Yamaguchi Prefectural Grand Medical Centre
- Yamaguchi University Hospital

The study protocols received approval from the certified review board, institutional review boards, and ethics committees at Yamaguchi University Hospital (CRB6180002). Informed consent was obtained from all participants and their legal guardians, and the research was conducted in accordance with the principles of the Declaration of Helsinki.

Study Timeline

Enrolment Period: January 1, 2016, to December 31, 2019 **Scheduled Study Period**:
January 1, 2016, to March 31, 2021
First Patient Enrolment: January 25, 2017
Final Enrolment Date: January 30, 2026
This version presents the study's details in a structured and clear manner.

Participants: Here's a refined version of your description of the inclusion and exclusion criteria for the RELAND study:

Inclusion and Exclusion Criteria for the RELAND Study

Inclusion Criteria: Patients eligible for the study had to meet the following criteria: Presence of definite retinal thickening due to naïve diabetic macular edema (DME), as confirmed through clinical examination techniques including slit-lamp examination, fundus examination, and optical coherence tomography (OCT).Patients who met all inclusion criteria and none of the exclusion criteria were enrolled in the study (refer to Supplementary Table S1).**Exclusion Criteria**: The study excluded patients with vitreomacular traction syndrome, which encompasses conditions such as vitreomacular adhesions and epiretinal membranes. This version maintains clarity and organization, making it easier to understand the study's criteria.

Procedures: -
Here's a polished version of your description of the study's consent process and follow-up examinations: **Study Procedures and Follow-Up**All patients provided written informed consent prior to enrolment in the study. Throughout the study, participants underwent monthly evaluations that included:

- Best-Corrected Visual Acuity (BCVA)
- Intraocular Pressure (IOP)
- Optical Coherence Tomography (OCT)
- Slit-Lamp Examinations

Patients were treated according to the study protocol during the initial visits (Visits 1 to 6). From Visits 7 to 12, treatment decisions were made at the discretion of the attending physician (refer to Supplementary Fig. S1 for the study timeline). This version is concise and clearly outlines the consent process and follow-up protocol. If you need further modifications or additional details, feel free to let me know! Here's a refined version of your description of the upload phase and patient group assignments in the RELAND study:
Upload Phase and Patient Group Assignments

During the upload phase (Visits 1 to 3), all patients received three doses of 0.5 mg Ranibizumab intravitreal therapy (IVT) at a frequency of 0.5 mg per month. Following this phase, eyes were categorized into either the responder or non-responder groups based on changes in Best-Corrected Visual Acuity (BCVA) and/or central

foveal retinal thickness (CRT) compared to baseline measurements. The criteria for group assignment were as follows:
Responder Group: Defined by a BCVA improvement of ≥ 5 letters and/or a CRT improvement of ≥ 20%.

- **Non-Responder Group**: Defined by a BCVA improvement of < 5 letters and a CRT improvement of < 20% from Visits 1 to 4. For patients in the non-responder group, further classification was made at Visit 4 based on the presence of microaneurysms (MAs) involved in macular Edema, as determined by fluorescein angiography (FA). These patients were then assigned to either the laser combination therapy or Ranibizumab monotherapy group.This version clearly outlines the processes and criteria used in the study. If you need further adjustments or additional details, just let me know!
-
Here's a refined summary of the treatment protocols for the responder and non-responder groups during the maintenance phase of the RELAND study:

Treatment Protocols During the Maintenance Phase

Responder Group: Patients in this group received intravitreal therapy (IVT) with Ranibizumab during the maintenance phase (Visits 4 to 6) if their central foveal retinal thickness (CRT) was greater than 250 µm.
Laser Combination Therapy Group: Patients assigned to this group underwent focal laser treatment for microaneurysm (MA)-induced Edema at Visit 4. The laser photocoagulation was performed according to the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol, with the following criteria adjusted for each individual eye:
- **Wavelength**: Yellow

- **Duration**: 0.1 seconds

- **Spot Size**: 50 µm

- **Power**: 100 mW

Laser treatment was not administered within a 500 µm zone of the fovea. Additional laser treatments could be performed after Visit 7 based on the physician's discretion. This group was also eligible for Ranibizumab IVT during the maintenance phase if CRT remained greater than 250 µm.

Ranibizumab Monotherapy Group: Patients in this group had eyes that did not exhibit MA leakage associated with macular Edema, or those with MA leakage confined to the central 500 µm. They received Ranibizumab IVT during the maintenance phase if their CRT was greater than 250 µm. Here's a refined summary of the patient screening and treatment protocol in the RELAND study:

Patient Screening and Treatment Protocol
Patients were screened within four weeks prior to study enrolments. Eligible participants received intravitreal injections of biosimilar Ranibizumab at a dose of 0.5 mg every four weeks for a total of 24 weeks, amounting to six doses. Each enrolled patient was scheduled for a total of 16 study visits, which included the screening visit and the end-of-study visit (see Fig. 1). Follow-up evaluations were conducted the day after each administration of the study drug. This version presents the information clearly and concisely.

Treatment: -
Here's a polished version of your text regarding the patient screening and treatment protocol:
Patient Screening and Treatment Protocol

Patients were screened within four weeks prior to study enrolments. Eligible participants received intravitreal injections of biosimilar Ranibizumab at a dose of 0.5 mg every four weeks for 24 weeks, totalling six doses. Each enrolled patient was scheduled for 16 study visits, which included the screening visit and the end-of-study visit (see Fig. 1). Follow-up evaluations were conducted the day after each administration of the study drug. This version maintains clarity and conciseness.

Safety assessments: -
Here's a refined summary of the safety endpoints and examination protocols in the RELAND study:

Safety Endpoints and Examination Protocols
Safety Endpoints: The study evaluated several safety endpoints, including:
- Incidence of adverse events (AEs) and serious adverse events (SAEs), including hypersensitivity reactions and significant laboratory abnormalities.
- Proportion of patients developing anti-ranibizumab antibodies after six months of treatment.

Examinations:

Fundus Fluorescein Angiography (FFA): Conducted for all patients on the day of screening to assess lesion severity.

**Spectral Domain-Optical Coherence Tomography (SD-OCT) **: Performed on the day of screening, at baseline, and at 3- and 6-months post-treatment.
Slit-Lamp Examination and Indirect Ophthalmoscopy: Conducted at screening, during each dose administration visit, and at the end of the study.

Intraocular Pressure Measurements: Taken at the same visits as slit-lamp examinations.

Ophthalmic Examination: Conducted the day after dosing using a safety questionnaire (see Additional file 1: Appendix S1). This version organizes the information clearly and maintains a professional tone. Let me know if you need any further changes or additional information!

Immunogenicity assessments: -
Here's a refined version of your text regarding the evaluation of immunogenicity and the sample collection process:

Immunogenicity Assessment
Immunogenicity was evaluated by assessing the presence of serum anti-ranibizumab antibodies in all patients. A total of nine samples (baseline, Weeks 2, 4, 6, 8, 12, 16, 20, and 24), each consisting of 6 mL, were collected from each patient for the detection of anti-ranibizumab antibodies in serum.

Sample Collection Process:

- Blood samples were collected via venipuncture with the patient's arm in a downward position, using vacutainers placed upright in a rack kept in an ice-cold water bath until centrifugation. The serum was separated by centrifugation at 3000 ± 100 rpm for 10 minutes at room temperature (18–25 °C).
-
- Following centrifugation, the serum samples were transferred into polypropylene cryovials using a pasture pipette (dropper), with approximately 500 µL in the first aliquot and the remaining volume in the second aliquot. The samples were stored at a temperature of −22 °C
± 5 °C or below for interim storage until shipment for analysis. For transport, the samples were packed with dry ice and maintained at a controlled temperature of −22 °C ± 5 °C or below, accompanied by a data logger to monitor conditions during transit. This version clarifies the immunogenicity evaluation process and organizes the information for better readability.

Efficacy assessments: -
Here's a refined summary of the efficacy assessments in the study:

Efficacy Assessments
Efficacy was evaluated at baseline, Week 12, and at the end of the study (Week 24) using the following parameters:

Best-Corrected Visual Acuity (BCVA): Assessed using the ETDRS visual acuity chart. Key metrics included:

The proportion of patients who lost fewer than 15 letters (approximately three lines) from baseline visual acuity by the end of the study.

The mean increase in BCVA in the study eye from baseline to the end of the study. **Central Retinal Thickness (CRT)**: Measured using spectral domain optical coherence tomography (SD-OCT) in the study eye. Changes in retinal thickness from baseline to the end of the study were calculated.

**Visual Function Questionnaire (VFQ-25) **: Changes in the VFQ-25 score from baseline to the end of the study were also assessed. This version presents the efficacy assessments clearly and concisely. If you need further modifications or additional details, feel free to let me know.

RESULTS:

Patient disposition: -
Here's a polished summary of the patient screening and enrolment process:

Patient Screening and Enrolment

A total of 149 patients were screened across 16 centres in India. Out of these, 126 patients were enrolled in the study, while 23 were excluded for the following reasons:
Did not meet the selection criteria: 11 patients

We're not ready to provide consent for study participation: 12 patients

All 126 enrolled patients received biosimilar Ranibizumab and were included in the safety and immunogenicity populations. The intention-to-treat (ITT) population included 125 patients, as one patient did not have any post-dose efficacy assessment due to a protocol deviation.

Demographics and baseline characteristics: -
Of the 126 enrolled patients, 116 (92.06%) completed the study and were included in the per-protocol (PP) population. The 10 patients who did not complete the study were unable to return for follow-up (n = 1), died (n = 1), missed a visit (n = 1), had the investigator's decision (n = 1), or withdrew consent (n = 6) (see Fig. 2). This version maintains clarity and provides a comprehensive overview of the screening and enrolment process. If you need any further changes or additional details, just let me know.

Biosimilar ranibizumab exposure: -.
Here's a refined summary of the dosing information for the enrolled patients:

Dosing Information

All 126 enrolled patients received at least one dose of biosimilar Ranibizumab. The distribution of doses among the patients was as follows:
**120 patients (95.24%) ** received all 6 doses, totalling 3 mg.

**4 patients (3.17%) ** received 4 doses, totalling 2 mg.

1 patient received 5 doses, totalling 2.5 mg.
1 patient received only 1 dose, totalling 0.5 mg.

This version clearly presents the dosing data, making it easy to understand the treatment compliance among the patients.

Safety: -
Here's a refined summary of the adverse events (AEs) reported in the study:

Adverse Events (AEs)
Of the 126 enrolled patients, 16 (12.7%) reported a total of 19 adverse events during the study (see Table 2). Notably, one patient with a history of hypertension and asthma, who had experienced a myocardial infarction (MI) four months prior to screening, died following the fourth dose of biosimilar Ranibizumab due to another MI event that was unrelated to the study drug. Aside from this case, no other patients discontinued the study due to an adverse event, and there were no other serious adverse events (SAEs) reported. This version presents the information clearly and concisely. If you have any further changes or additional details to include, just let me know.

Here's a polished summary of the adverse events (AEs) related to the study drug:
Adverse Events (AEs) Related to Study Drug
Out of the 19 AEs reported, only two—iridocyclitis and an increase in intraocular pressure— were considered related to the study drug.
Intraocular Pressure (IOP) Changes:
- The mean ± SD IOP (mm Hg) decreased from baseline:
  - Left Eye: from 14.5 ± 3.38 to 13.9 ± 2.74
  - Right Eye: from 14.2 ± 3.19 to 13.9 ± 2.97 at Week 24.

Severity of AEs:
- The majority of AEs were mild (n = 15).
- Three AEs (corneal Edema, iridocyclitis, increase in intraocular pressure) were moderate.
- One AE (death) was classified as severe.
- Except for the death, all other AEs resolved during the study. **Ocular and non-ocular AEs**:
- Out of the 19 AEs, 10 were ocular, reported by 9 patients (7.14%). The most common ocular AE was an increase in intraocular pressure (4 AEs in 3 patients), followed by eye pruritus (2 AEs in 2 patients). The most common non-ocular event was pyrexia, reported as 5 AEs in 5 patients (3.97%). No hypersensitivity reactions to biosimilar Ranibizumab were reported during the study. This version organizes the information clearly and presents the findings in a concise manner.

Efficacy: -
Here's a refined summary of the visual acuity improvements observed in the study:

Visual Acuity Improvements

At the end of 24 weeks, visual acuity in the treated eye showed significant improvement in both the intention-to-treat (ITT) and per-protocol (PP) populations, as assessed by various efficacy parameters including the proportion of patients with less than 15-letter loss, best- corrected visual acuity (BCVA), central retinal thickness (CRT), and the Visual Function Questionnaire (VFQ-25) score.

Key Findings:

Proportion of Patients Losing Fewer than 15 Letters:

ITT Population:

Week 12: 98.40% (95% CI 96.20%, 100.60%)

Week 24: 97.60% (95% CI 94.92%, 100.28%)

PP Population:

Week 12: 98.28% (95% CI 95.91%, 100.64%)

Week 24: 97.41% (95% CI 94.53%, 100.30%)

Mean BCVA Improvements:

- **ITT Population**:
  - Baseline: 44.0 (16.27) letters
  - Week 12: 50.3 (17.37) letters (mean [SD] difference 6.3 [11.11] letters, p < 0.0001)
  - Week 24: 53.7 (17.83) letters (mean [SD] difference 8.8 [13.61] letters, p < 0.0001)
- **PP Population**:
  - Baseline: 44.4 (16.38) letters
  - Week 12: 50.8 (17.17) letters (mean [SD] difference 6.5 [11.31] letters, p < 0.0001)
  - Week 24: 53.5 (17.84) letters (mean [SD] difference 9.2 [13.85] letters, p < 0.0001)

These results demonstrate significant improvements in visual acuity for both populations throughout the study period. This version organizes the data clearly and emphasizes the significant findings. If you need any further changes or additional information, just let me know.

DISCUSSION:

Here's a polished summary of the ASSET study findings regarding the biosimilar ranibizumab (Razumab™):
ASSET Study Overview

The ASSET study was a Phase 4, single-arm, post-marketing, prospective study designed to evaluate the safety and efficacy of Razumab™, the world's first biosimilar ranibizumab, in patients with wet age-related macular degeneration (AMD).
Key Findings:

- **Safety**: Razumab™ was well-tolerated among patients with wet AMD, demonstrating a safety profile comparable to that of the innovator ranibizumab, as reported in the literature.
- **Efficacy**: The study confirmed that biosimilar ranibizumab effectively improved the overall condition of wet Additionally, the efficacy and safety of biosimilar ranibizumab were previously supported by real-world retrospective studies, RE-ENACT and RE-ENACT 2, which included patients with various macular disorders, including wet AMD. This summary effectively captures the essence of the ASSET study.

Here's a refined summary of the study population and treatment regimen:

*Study Population and Treatment Regimen**

In this study, we enrolled 126 patients, regardless of gender, aged 50 years or older, who had a best-corrected visual acuity (BCVA) ranging from 20/40 to 20/320 as assessed by the ETDRS chart. All participants exhibited active sub-foveal choroidal neovascularization (CNV) in the study eye, a critical factor associated with severe vision loss or blindness in wet age-related macular degeneration (AMD) patients. The selection criteria for the study population were informed by findings from the innovator's ANCHOR, MARINA, HARBOR, PIER, and SUSTAIN studies, which established the effectiveness of treatment regimens in wet AMD patients. Notably, the ANCHOR and MARINA studies demonstrated that a monthly ranibizumab regimen yields better outcomes compared to less frequent dosing strategies observed in the HARBOR, PIER, SUSTAIN, and IVAN studies. Consistent with these findings,our cohort received a monthly regimen of 0.5 mg intravitreal biosimilar ranibizumab. This version clearly outlines the study population and the rationale for the treatment regimen. If you need further adjustments or additional details, just let me know.

CONCLUSIONS:

Here's a concise summary of the findings from the ASSET study**Summary of ASSET Study Findings**The ASSET study evaluated the safety and efficacy of Razumab™, the world's first biosimilar ranibizumab, in patients with wet age-related macular degeneration (AMD) over a 6-month period. The results indicated that biosimilar ranibizumab exhibited a safety and efficacy profile comparable to that of the innovator ranibizumab, with no new safety concerns identified. Improvements were observed in patients with wet AMD, as assessed by visual acuity, best-corrected visual acuity (BCVA), and retinal thickness, specifically regarding the 15-letter loss metric. Future long-term studies with larger patient populations may provide further insights and

validation of these results. This summary effectively captures the key findings of the study.

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