2 Synopsis

Name of product: Brolucizumab (RTH258)

Protocol identification number: CRTH258C2302

Title of study: An Eighteen-Month, Two-Arm, Randomized, Double-Masked, Multicenter, Phase III Study Assessing the Efficacy and Safety of Brolucizumab versus Aflibercept in Adult Patients with Visual Impairment due to Macular Edema secondary to Central Retinal Vein Occlusion (RAVEN)

Investigator(s): 5.1.2.e , Tianjin Medical University Eye Hospital, No.251 Fukang Road, Nankai district, Tianjin, China

Study center(s): Australia (7 centers), Canada (5 centers), China (14 centers), Czech Republic (4 centers), France (5 centers), Germany (10 centers), Greece (2 centers), Hungary (4 centers), Israel (4 centers), Italy (4 centers), Japan (9 centers), Malaysia (2 centers), Netherlands (1 center), Russian federation (4 centers), Spain (6 centers), Thailand (3 centers), Turkey (1 center), United Kingdom (5 centers), and the United States (32 centers)

Publication (reference): None

Study period

Study initiation date: 03-Jul-2019 (first subject first visit)

Early termination date: 28-May-2021

Study completion date: 26-Jul-2021 (last subject last visit)

Phase of development (phase of this clinical study): III

Objectives: the primary and secondary objectives of the study are as following:

Objective(s)	Endpoint(s)
Primary objective	**Endpoint for primary objective**
• To demonstrate that brolucizumab is non-inferior to aflibercept with respect to the change in best-corrected visual acuity from baseline up to Month 6	• Change from baseline in BCVA at Week 24
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To assess the effect of brolucizumab as compared to aflibercept on BCVA	• Change from baseline in BCVA averaged over Week 40 to Week 52 and Week 64 to Week 76 • Change from baseline in BCVA by visit up to Week 76 • Proportion of study eyes with a gain ≥ 5, 10 and 15 letters in BCVA by visit compared to baseline • Proportion of study eyes with a loss ≥ 5, 10 and 15 letters in BCVA by visit compared to baseline
• To evaluate the anatomical outcome with brolucizumab relative to aflibercept	• Change from baseline in central subfield thickness (CSFT) averaged over Week 40 to Week 52 and Week 64 to Week 76 • Change from baseline in CSFT by visit up to Week 76 • Proportion of study eyes with presence of retinal fluid (intra- and/or subretinal fluid) by visit up to Week 76 (derived from SD-OCT) • Proportion of study eyes with a CSFT < 300 µM by visit up to Week 76
• To evaluate the treatment frequency with brolucizumab during the individualized	• Number of injections between Week 24 and Week 52 and between Week 24 and Week 76

Objective(s)	Endpoint(s)
flexible treatment (IFT) period relative to aflibercept	• Time to first re-treatment between Week 24 and Week 76
• To assess the safety and tolerability of brolucizumab relative to aflibercept	• Incidence of ocular and non-ocular AEs up to Week 52 and Week 76
• To evaluate the effect of brolucizumab relative to aflibercept on patient-reported vision-related quality of life	• Change from baseline in patient reported outcomes (NEI VFQ-25) at Week 24, Week 52 and Week 76
• To assess the immunogenicity of brolucizumab	• Anti-drug antibody status at baseline and Week 4, Week 12, Week 24, Week 36, Week 52 and Week 76

Methodology: The study was an 18-month, randomized, double-masked, multi-center, active-controlled, non-inferiority, 2-arm study in subjects with visual impairment due to macular edema secondary to central retinal vein occlusion (CRVO).

Subjects who met all the inclusion and none of the exclusion criteria were randomized in a 1:1 ratio to one of the two treatment arms as following:

- Brolucizumab 6 mg: 6 x q4w followed by 48 weeks of individualized flexible treatment (IFT) from Week 24 onwards
- Aflibercept 2 mg: 6 x q4w followed by 48 weeks of IFT from Week 24 onwards

The study comprised of a Screening period (Day -28 to Day -1), Double-masked treatment period (Day 1 to Week 72) and Post-treatment follow-up period (Week 72 to Week 76).

Number of subjects (planned and analyzed): 750 subjects (375 subjects per arm) were planned to be enrolled; overall, 493 patients were included in the randomized analysis set.

Diagnosis and main criteria for inclusion: The study included male and female patients aged ≥ 18 years diagnosed with visual impairment due to macular edema secondary to CRVO. If both eyes were eligible as per the inclusion and exclusion criteria, the eye with the worse visual acuity was selected for study eye, unless the investigator deemed it more appropriate to select the eye with better visual acuity, based on medical reasons or local ethical requirements.

Key inclusion criteria

- Signed informed consent was to be obtained prior to participation in the study
- Patients with visual impairment due to macular edema secondary to CRVO diagnosed < 6 months prior to screening; hemiretinal vein occlusion was classified as CRVO for the purpose of this trial (study eye)
- BCVA score between 78 and 23 letters, inclusive, using ETDRS visual acuity testing charts (approximate Snellen equivalent of 20/32 to 20/320) at both screening and baseline visit (study eye)

Duration of treatment: The planned duration of study was 76 weeks. At the time of study termination, approximately, 60%, 50%, and 25% of the subjects completed the study treatment after Week 24, Week 52, and Week 72, respectively.

Test and reference therapies, dose and mode of administration, batch number: Brolucizumab was provided in a single use, sterile glass vial to deliver a 6 mg dose when administering a volume of 0.05 mL. Aflibercept was provided in a single use, sterile glass vial to deliver a 2 mg dose when administering a volume of 0.05 mL. Study treatment batch numbers are provided in the below table:

Study drug and strength	Batch number
Brolucizumab 6 mg liquid in vial 0.05 mL	5.1.1.c [redacted]
Aflibercept 2 mg liquid in vial 0.05 mL	5.1.1.c [redacted]

Criteria for evaluation

Efficacy: The following assessments were performed to evaluate the effect of brolucizumab and aflibercept on visual function, retinal structure and vascular leakage:

- BCVA with ETDRS-like charts at an initial testing distance of 4 meters
- 5.1.1.c

Safety: 5.1.1.c .

Patient reported outcomes: 5.1.1.c

Anti-drug antibody assessments (Immunogenicity) and systemic exposure: 5.1.1.c

Statistical methods: The objective related to the primary endpoint was to demonstrate non-inferiority of brolucizumab versus aflibercept with respect to the change from baseline in BCVA at Week 24, assuming a non-inferiority margin of 4 ETDRS letters. An analysis of variance (ANOVA) model was used to test non-inferiority. The same approach for non-inferiority assessment in change from baseline in BCVA at Week 24 was applied to sensitivity analysis and supplementary estimand.

Summary statistics were presented by treatment group unless otherwise specified.

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Summary – Results

Demographic and background characteristics:

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Efficacy results

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Summary of impact of change(s) due to COVID-19 on efficacy

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Patient reported outcomes

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Safety results:

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Anti-drug antibody (Immunogenicity)

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Summary of impact of change(s) due to COVID-19 on safety results

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Conclusion:

- The primary hypothesis of non-inferiority of brolucizumab in improving the BCVA at Week 24 as compared to aflibercept in patients with macular edema due to CRVO was not established based on the primary method. The same conclusion was further confirmed by the supportive and sensitivity analyses.
- Higher incidences of ocular SAEs and AESIs in the study eye were reported in the brolucizumab arm compared to the aflibercept arm and support the decision of early study termination.

History of changes to the synopsis			
Version	Date (content final)	Summary of Changes	Change to overall conclusion
1.0	28-Mar-2022	Original version	NA
2.0	11-Jul-2022	Antidrug antibody analyses and the summary results for antidrug antibody are included to the synopsis.	No