A First in Human trial to study safety and tolerability of single rising intravitreal doses (oPen label, non-randomized, uncontrolled) and in Addition the early biological Response of mulTiple intravitreal doses (double-masked, RandomIzed, shamcontrolleD) of BI 765128 in panretinal photocoaGulation (PRP) treated diabetic rEtinopathy (DR) patients with diabetic macular ischemia (DMI) - the PARTRIDGE Study

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Diabetic Macular Ischemia (DMI) is a complication of diabetic retinopathy (DR) and can lead to vision loss. Currently, there are no approved or effective treatments to prevent either onset or progression of DMI in DR patients.As a transition from...

Ethical review	Approved WMO
Status	Completed
Health condition type	Ocular haemorrhages and vascular disorders NEC
Study type	Interventional

Summary

ID

NL-OMON53613

Source
ToetsingOnline

Brief title
1451-0001: PARTRIDGE study

Condition

- Ocular haemorrhages and vascular disorders NEC

Synonym
Diabetic Macular Ischemia, DMI

Research involving
Human

Sponsors and support

Primary sponsor: Boehringer Ingelheim
Source(s) of monetary or material Support: De Opdrachtgever Boehringer Ingelheim

Intervention

Keyword: BI 765128, Diabetic macular ischemia, Diabetic retinopathy

Outcome measures

Primary outcome

Part A:

- Number of subjects with ocular dose limiting events (DLEs) from drug

administration until day 8 (7 days after treatment)

Part B:

- Number of subjects with drug-related AEs from drug administration until EOS

Secondary outcome

Part A:

- Number of subjects with drug related AEs at EOS

- Number of subjects with any ocular AEs (eye disorders) at EOS

Part B:

- Change from baseline of the size of the FAZ in optical coherence tomography

angiography (OCTA) at visit 5

- Change from baseline of the size of the FAZ in optical coherence tomography angiography (OCTA) at visit 6

- Change from baseline of the size of the FAZ in optical coherence tomography angiography (OCTA) at visit 7

- Change from baseline of BCVA at Visit 7

- Number of subjects with any ocular AEs (eye disorders) from drug administration until EOS

Study description

Background summary

Diabetic retinopathy (DR) can cause visual loss in a number of ways. Microvascular changes due to hyperglycemia lead to increases in permeability, and thus extravascular exudation and fluid accumulation in the macula (diabetic macular edema, DME). Similarly, alterations of micro-vessels can lead to retinal non-perfusion and ischemia. Consequently, a dramatic increase of vascular endothelial growth factor (VEGF) drives the formation of retinal new vessels (proliferative diabetic retinopathy, PDR), which eventually bleed, and cause a sudden decrease in vision (vitreous hemorrhage). In both conditions, VEGF plays a fundamental role, and anti-VEGF agents are effective in improving both DME and DR. For patients with PDR, panretinal photocoagulation (PRP) is the current standard of care. Patients with severe non- proliferative diabetic retinopathy (NPDR) and a high risk of developing PDR can also benefit from PRP to prevent progression of retinopathy. PRP destroys the ischemic retina, (the major source of VEGF), and thus prevents the formation of new vessels, or promotes their regression.

In some patients, however, in the absence of DME, after successful treatment with PRP, with no evidence of active new vessels, the visual acuity continues to decrease.

Some reports have suggested increasing ischemia in the central part of the retina, the macula, as a possible explanation. In this condition, called diabetic macular ischemia (DMI), the retinal tissue may not receive enough nutrients leading to retinal tissue loss and permanent and irreversible vision loss. In DMI, anti-VEGF therapy is not effective, and destructive laser photocoagulation cannot be applied.

Previously, DMI was observed and diagnosed by means of fluorescein angiography (FA) using an intravenous dye. It was defined as an abnormal enlargement of the foveal avascular zone (FAZ). In patients with diabetic retinopathy, FA may show an abnormal enlargement of the FAZ, which is the most common definition of DMI. Recently, optical coherence tomography angiography (OCTA) has emerged which can visualize the retinal blood vessels and hence ischemia in greater detail. OCTA is non-invasive and multiple levels of the capillary plexus can be visualised. OCTA can measure the area of the FAZ. Moreover, the FAZ measured by FA corresponds well with the FAZ measured by OCTA (R17-3317). For these reasons OCTA is likely to become the gold standard in the diagnosis and monitoring of DMI.

There are many unknowns related to DMI. Since this condition is associated with a progressive loss of neural tissue, it can be hypothesized that restoration of the macular vasculature before retinal degeneration occurs could be a key objective for these patients and prevent permanent vision loss. There are currently no treatments available for DMI making it an urgent unmet need.

Study objective

Diabetic Macular Ischemia (DMI) is a complication of diabetic retinopathy (DR) and can lead to vision loss. Currently, there are no approved or effective treatments to prevent either onset or progression of DMI in DR patients.

As a transition from preclinical investigations to clinical development in this first-in human trial, the safety, tolerability, pharmacokinetics and early biological response of BI 765128 will be investigated in volunteer subjects with DMI.

This trial will include subjects affected by DMI with significant visual loss since intravitreal injections in subjects without the condition would not be considered ethically justifiable.

Study design

This trial will consist of two parts, A and B. Part A will be nonrandomized, open-label and uncontrolled. Part B will be doublemasked, randomized and sham-controlled (ratio 2:1). The Netherlands will participate in part B.

Intervention

This trial will consist of two parts, Part A and Part B.

Cohorts of subjects will receive escalating doses of BI 765128, with the starting dose of 0.5 mg. The other dose level is 1 mg and the maximum planned dose is 2.5 mg.

For any dose-escalation cohort, at least 3 evaluable subjects will be required. Each cohort will
consist of newly enrolled subjects.

Dosing of subjects will be done in the following order:
- Cohort 1, 0.5 mg (number=3)
- Cohort 2, 1 mg (number=3)
- Cohort 3, 2.5 mg (number=6)

Part B of the study will only start if the highest dose is tolerated. Once the last subject in the highest dose cohort of Part A has attended visit 5 (day15) the SMC will meet and evaluate all DLE data as well as available systemic and ophthalmological safety data. The decision on whether to proceed to Part B will be taken based on the occurrence of DLEs.

In Part B, the highest dose will be used (2.5mg). Thirty subjects will be recruited, 2:1 ratio of active treatment versus sham. Subjects dosed in Part A of the trial will not be included.

Subjects will be randomized to receive either active treatment or sham injection. In Part B, subjects will receive three consecutive doses/sham injections over a 3-month period (once every 4 weeks). All subjects included in the part B of the trial, will be observed for safety and efficacy for 12 weeks after the last injection.

Part B will provide information about the early biological response of BI 765128 by comparing the treated group to the sham group.

Study burden and risks

Burden/ possible risk:
- Worsening of the disease
- Patient may experience side effects or adverse events of the study drug
- Patient may experience discomfort due to the procedures and measurements during the study
- Additional procedures and measurements will be performed (outside SoC), as described in the protocol
- Participating in the study will take extra time
- Patient needs to adhere to the study schedule

The procedures that will be performed in this study are described in section E4, E5 and E6 of this ABR.

Possible benefit:
- The study medication may improve the symptoms associated with DMI
- Participation in the study helps researchers gain a better understanding of the disease.

See section 1.4 of the protocol for the benefit-risk assessment.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Part B:
• Panretinal photocoagulation-treated DR patients with either no or inactive retinal neovascularization per investigator judgement
• Presence of significant DMI: Large foveal avascular zone (FAZ) defined as those with >=0.5mm2 area present on OCTA. If FAZ is <0.5mm2 then an enlarged peri-foveal inter-capillary space in at least 1 quadrant will be sufficient.
• Best-corrected VA <=85 letters (20/20) in the study eye

Exclusion criteria

Part B:
• Diabetic Macular Edema (DME), defined as a CST >= 305µm for men and >= 290 µm for women (Optovue Angiovue) in the study eye
• Subjects receiving IVT injections for active DME (anti-VEGF, steroids) and macular laser in the previous 3 months to screening in the study eye
• History of vitrectomy in the study eye

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	24-02-2023
Enrollment:	1
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Not available
Generic name:	Not available

Ethics review

Approved WMO Date:	06-07-2022
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-10-2022
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	19-01-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	27-01-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-04-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-05-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2020-005425-87-NL
ClinicalTrials.gov	NCT04919499
CCMO	NL81392.100.22

Study results

Date completed: 07-08-2023

Results posted: 28-06-2024

First publication
10-04-2024