A safety study of intravitreal PP-001 in patients with chronic, non-infectious uveitis having chronic inflammation

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To assess the safety and tolerability of ascending doses of PP-001 whenadministered as a single intravitreal injection from 0,3 *g, 0,6 *g and 1,2*g with the option of an addition cohort with a dose of 2,1 *g PP-001.To assess the efficacy of...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Eye disorders
Study type	Interventional

Summary

ID

NL-OMON48871

Source
ToetsingOnline

Brief title
PP-001-1001

Condition

- Eye disorders

Synonym
inflammation, uveitis

Research involving
Human

Sponsors and support

Primary sponsor: Panoptes Pharma
Source(s) of monetary or material Support: Panoptes Pharma GmbH

Intervention

Keyword: First in Man, intravitreal injection, Safety, Uveitis

Outcome measures

Primary outcome

Primary

* Safety parameters (i.e., changes in clinical signs and symptoms from

ophthalmic exam, and AEs)

Secondary outcome

Secondary

* Improvement of inflammation or of any other parameter determined at the

ophthalmic examination following the injection of PP-001

* The concentration of PP-001 in plasma at Screening, 4 h ± 1 h after dosing

and on Day 2

Study description

Background summary

PP-001 is indicated for the treatment of non-infectious uveitis (NIU). Uveitis is a chronic or relapsing intra-ocular inflammatory disease that affects the uvea (composed of the iris, choroid and ciliary body), retina, vitreous body, optic nerve head, retinal pigment epithelium and the anterior chamber, but may also involve adjacent structures, including the sclera or cornea.
The integrity and transparency of the ocular media (aqueous, lens and vitreous) and ocular tissue (iris, ciliary body, retina, pigment epithelium and choroid) are critical for optimal visual function because they refract, transmit, regulate and sense light. Any distortion of the visual axis by inflammatory processes within the eye can adversely affect vision. Uveitis is a disease with symptoms ranging from temporary effects, including discomfort, pain or blurring of vision, to permanent defects in visual acuity and visual field due to irreversible tissue damage and even blindness. Visual impairment may result from direct damage to any ocular structure (e.g., cataracts, glaucoma, macular

oedema.
Uveitis can be caused by infections or by autoimmune disease. Non-infectious uveitis covers all uveitis cases, which are considered to be of autoimmune or autoinflammatory origin including systemic immunological disease-associated uveitis. It also includes acute and chronic uveitis, as well as relapsing forms, and may occur at any location in the eye.
The main treatment strategies for NIU involve the suppression of local inflammation. Treatments range from topical therapy (commonly corticosteroid eye drops) to systemic immunosuppression with either corticosteroids or steroid-sparing immunomodulatory therapeutic agents. Topical medication is generally only used to treat uveitis that affects the anterior part of the eye (i.e. anterior chamber). Patients suffering from intermediate and/or posterior uveitis (i.e. that which affects the vitreous body and retina/choroid) are routinely treated with high doses of systemic corticosteroids. Dosing of corticosteroids depends on the timeframe and severity of inflammation. Usually, the initial treatment includes high-dose corticosteroids, which is then slowly tapered according to disease activity. The ultimate expected therapeutic role of PP-001 will be as a steroid-sparing agent and allow steroid doses to be tapered quickly. Due to its underlying mode of action, PP-001 is suitable for the treatment of NIU only.

Study objective

To assess the safety and tolerability of ascending doses of PP-001 when administered as a single intravitreal injection from 0,3 *g, 0,6 *g and 1,2 *g with the option of an addition cohort with a dose of 2,1 *g PP-001.

To assess the efficacy of ascending doses of PP-001 when administered as a single intravitreal injection from 0,3 *g, 0,6 *g and 1,2 *g with the option of an addition cohort with a dose of 2,1 *g PP-001.

Study design

This prospective, multi-centre, open-label, non-randomized, consecutive study will be conducted in accordance with the European Union (EU) Clinical Trial Directive 2001/20/EC and 2005/28/EC, The Medicines for Human Use (Clinical Trials) Regulations 2004 and current amendments, the Declaration of Helsinki (revised version of Edinburgh, Scotland 2000), Good Manufacturing Practice (GMP), Good Clinical Practice (GCP) and the current national regulations and guidelines, approved by both the local ethics committee and regulatory authority.

Eighteen patients at the age of 18 and older will be enrolled and receive a single intravitreal injection of PP-001. Patients must have chronic, posterior uveitis, intermediate uveitis or panuveitis requiring treatment and have been receiving an adequate therapy of e.g. systemic corticosteroid treatment or

immunosuppressive therapy (e.g. azathioprine, methotrexate, cyclosporine, mycophenolate, tacrolimus) or any combination thereof. Any systemic therapy at study start should be continued throughout the study. Patients must have best-corrected Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity of 10 letters or better (approximately 1/35 or 0.032) but equal or less than 70 letters (approximately 20/40 or 0.5) in the study eye.
Patients must give written consent for the study before any study assessments are performed. Screening assessments will be performed up to 14 days before dosing. Baseline assessments will be performed no more than 7 days before injection. In case screening visit and baseline visit are on the same day (-7 up to dosing), examinations scheduled for both visits need only to be performed once and may be used for both study visits. The study will involve seven study visits (Screening, Baseline, the day of injection (Day 0) and Days 2, 7, 14, and 28) and telephone calls on Day 1 and Day 40.
Patients will be divided into three cohorts of four patients and will receive the following treatments administered as a single intravitreal injection:
* Cohort 1 will receive 0.3 µg of PP-001
* Cohort 2 will receive 0.6 µg of PP-001
* Cohort 3 will receive 1.2 µg of PP-001
The patients within a cohort will be dosed consecutively with a minimum time interval of 7 days between the dosing of the previous patient and the dosing of the next patient. The results from each dosing day will be reviewed before progressing towards the subsequent dosing day. The next cohort will only receive PP-001 after the previous cohort has completed all study sessions up to Day 28 and no safety issues have been identified after reviewed by the Safety data management board (SDMB).
After 12 patients have been treated in the three cohorts and after all patients have finished the last follow up an interim analysis by the SDMB will be conducted to identify potential safety issues and to determine the highest tolerable dose. If no safety issue can be identified, then a fourth, higher dose will be given to a cohort of four patients (Cohort 4). The dose for a potential Cohort 4 will be 2.1 µg of PP-001.
If safety issues are identified in any of Cohorts 2, 3 or 4, two additional patients will receive the next lower dose.
Safety will be assessed by monitoring vital signs and recording of AEs (see Section 7). Safety procedures will be performed by the Investigator or suitably qualified individuals designated by the Investigator.
Pharmacokinetic sampling will take place at Screening, 4 h ± 1 h after injection and on Day 2.
Efficacy will be evaluated by ophthalmic examination.

Intervention

Patients will receive a single intraocular dose of PP-001.
The study treatment procedure must be performed only by the qualified Investigator in an operating room, surgical suite, or in an office setting using sterile technique. The study medication kit should be readily available

during the procedure. The final diluted PP-001 solution will be injected at the required dose at a volume of 100 µL. For safety reasons, an emergency pars plana vitrectomy aiming at removal of injected drug will be available in case of a severe adverse event including, but limited to, acute loss of visual acuity or acute inflammatory or toxic response to injection. It is therefore mandatory for patients to remain in the hospital for at least 4 hours after the injection procedure.

Study burden and risks

At this stage of development, toxicity of PP-001 in human eyes cannot be ruled out but the risk is considered low based on the safety factor calculated using preclinical data. Considering the expected low systemic exposure of PP-001, potential systemic side effects known from other DHODH inhibitors are not expected. In order to minimize this risk, the first patient will receive the lowest dose, which is approximately 90 times less than the established safe concentration in preclinical studies. The next patient will only receive an injection after a safety gap of 7 days and review of all data by the SDMB. The next highest dose will only be administered after the safety of the lower dose has been established.
The procedure of an injection into an inflamed eye has been established in other approved types of uveitis treatment such as Ozurdex and Retisert, in Phase III studies with sirolimus and the off-label use of intraocular triamcinolone. These studies have not shown any significant risks associated with eye injections. Concerns have been raised over the application of small crystals into the eye because of the potential to induce an autoinflammatory reaction. The type and structure of the preparation used in this study should reduce this risk.
Study PP-001-1001 will provide valuable data on the safety, tolerance and pharmacokinetic profile of PP-001 after single dosing in patients with severe uveitis, which will help to define the dose for future studies.
In conclusion, based on the currently available safety data, PP-001 has an acceptable benefit/risk profile in patients at doses in the estimated therapeutic range of 0.3*1.2 (2.1) µg/eye, and at the same time might reduce some of the inflammatory indices in patients with severe uveitis who have no treatment alternative.

Contacts

Public
Panoptes Pharma

Reisnerstrasse 34/1
Vienna 1030

AT
Scientific
Panoptes Pharma

Reisnerstrasse 34/1
Vienna 1030
AT

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Male or female patients at the age of 18 years and older who have diagnosis of chronic posterior uveitis, intermediate uveitis or panuveitis.
2. Good general state of health (mentally and physically). Laboratory parameters and vital signs of patients must be within the normal ranges.
3. A signed and dated written informed consent form.
4. A signed and dated written data protection consent form.
5. Female patients of childbearing potential must perform a negative urine pregnancy test prior to the injection on the day of the injection visit (Day 0).
6. Male and female patients must ensure that one highly effective method combined with an acceptable method of contraception is used for the entire duration of the study, from first dose up to the study follow-up visit, and refrain from becoming pregnant or fathering a child in the 3 months following the last study drug administration. Male patient must agree with their female partners prior to screening to use the above specified methods of contraception while receiving protocol-specified medication, and for 3 months after stopping the medication
7. Have diagnosis of chronic posterior uveitis, intermediate uveitis or panuveitis (as defined by the Standardization of Uveitis Nomenclature Working Group [Jabs et al., 2005]) in at least one eye. For patients with panuveitis, the anterior component of inflammation must be less than the posterior

component. The investigator to his best knowledge must rule out any suspected masquerade syndrome or infection prior to study entry.
8. Have chronic, posterior uveitis, intermediate uveitis or panuveitis requiring treatment.
9. Have media clarity, pupillary dilation and patient cooperation sufficient for adequate visualization of the optic nerve in the study eye.
10. Have been receiving an adequate therapy of e.g. systemic corticosteroid treatment or immunosuppressive therapy (e.g. azathioprine, methotrexate, cyclosporine, mycophenolate, tacrolimus) or any combination thereof. Any systemic therapy at study start should be continued throughout the study.
11. Best-corrected Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity of 10 letters or better (approximately 1/35 or 0.032) but equal or less than 70 letters (approximately 20/40 or 0.5) in the study eye
12. Best-corrected ETDRS visual acuity of 34 letters or better in the fellow eye (approximately 20/200 or 0.1)

Exclusion criteria

1. Patients in whom media opacities (cornea, anterior or posterior synechia, cataract, vitreous haze and others) of either eye preclude investigation and documentation of the posterior pole and intravenous fluorescein angiography, or optical coherence tomography evaluation in the study eye.
2. Patients receiving any local biologicals.
3. Treatment with cyclophosphamide or chlorambucil.
4. Intravitreal injections (including but not limited to anti-vascular endothelial growth factors) 60 days prior to the baseline.
5. Posterior subtenon's injection or orbital floor injection of steroids 90 days prior to Baseline.
6. Any implantable corticosteroid-eluting device (Ozurdex, Iluvien, Retisert, triamcinolone intravitreal implant, fluocinolone intravitreal implant) in the study eye, with the following exceptions:
* If the device had been removed more than 90 days prior to Day 0 of this study, the eye will be eligible for PP-001-1001.
* If Ozurdex had been implanted 6 months before Day 0 of this study, the eye will be eligible for PP-001-1001.
* If Iluvien or Retisert had been implanted 3 years before Day 0 of this study, the eye will be eligible for PP-001-1001.
7. Intraocular surgery within 90 days prior to Day 0 in the study eye.
8. Capsulotomy within 30 days prior to Day 0 in the study eye.
9. History of vitreoretinal surgery or scleral buckling within 90 days prior to Day 0 in the study eye.
10. Any ocular surgery (including cataract extraction or capsulotomy) of the study eye anticipated within the first 60 days following Day 0.
11. Intraocular pressure (IOP) *25 mmHg in the study eye (glaucoma patients maintained on no more than one topical medication with IOP <25 mmHg are allowed

to participate).
12. Ocular hypotonia (IOP less than 6 mmHg).
13. Pupillary dilation inadequate for quality fundus photography in the study eye.
14. Aphakia or anterior chamber lens in the study eye.
15. Visible scleral thinning, scleral ectasia or keratoconus in the study eye.
16. Presence of any ocular malignancy.
17. Ocular or periocular infection in either eye or the use of systemic antibiotics.
18. Participation in other investigational drug or device clinical trials within 90 days prior to Day 0, or planning to participate in other investigational drug or device clinical trials within 180 days following Day 0. This includes both ocular and non-ocular clinical trials.
19. Female patients who are pregnant, nursing, or planning a pregnancy, or who are of childbearing potential and not willing to use reliable means of contraception.
20. Use of any anticoagulant or thrombocyte aggregation inhibiting agent (marcumar, warfarin, heparin, enoxaparin, apixaban, rivaroxaban, pentosanpolysulfate, dabigatran) less than 7 days prior to injection visit (Day 0).
21. Known allergy or hypersensitivity to the study medication, any component of the delivery vehicle, any corticosteroids or any diagnostic agents used during the study (e.g., fluorescein, dilation drops, antibiotic drops, povidone).

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	5
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	not applicable
Generic name:	DHODH Inhibitor

Ethics review

Approved WMO Date:	28-11-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-02-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-03-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-04-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-04-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-06-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	17-07-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-08-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-09-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-04-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2016-000412-15-NL
CCMO	NL62850.078.17