Clinical Trial Protocol No. PP-001-1001

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

EudraCT Number 2016-000412-15

Version Date: 03. November 2017

Version Status: 3.1_GER

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

(Protocol PP-001-1001)

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PROTOCOL APPROVAL FORM

SUBMISSION OF PROTOCOL PP-001-1001

Title: **A safety study of intravitreal PP-001 in patients with chronic, non-infectious uveitis having chronic inflammation (Protocol PP-001-1001)**

03. November 2017

NAME	TITLE	DATE
Dr. Franz Obermayr	CEO, Panoptes Pharma	03. November 2017

Signature

INVESTIGATOR SIGNATURE PAGE

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

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In conducting this clinical study, I agree to be responsible for:

- Ensuring that the clinical investigation is conducted according to the World Medical Association Declaration of Helsinki (revised version of Edinburgh, Scotland, 2000, Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002), the guidelines of International Conference on Harmonization (ICH) Good Clinical Practice (CPMP/ICH/135/95), and other applicable local and national laws and requirements
- Protecting the rights, safety, and welfare of patients under my care
- Maintaining control of the drugs under investigation

I also agree to conduct the study as detailed in the protocol and in accordance with Panoptes Pharma GesmbH guidelines and all applicable government regulations. These guidelines and regulations include, but are not limited to:

- Permission to allow Panoptes Pharma GesmbH and regulatory agencies, to inspect study facilities and pertinent records at reasonable times and in a reasonable manner, which ensures patient confidentiality. If I am notified that this study is to be inspected by a regulatory agency, I will notify Panoptes Pharma GesmbH as soon as possible thereafter (no later than 1 week)
- Submission of the proposed clinical investigation, including the protocol, the informed consent documents, and any other patient materials required for study conduct, to a duly constituted Independent Ethics Committee (IEC)
- Obtaining written informed consent only after ensuring that the patient, or his/her legal representative, is competent to make the decision, understands what is contained in the informed consent document, and is consenting voluntarily. Written informed consent will be obtained prior to administration of study drug or any non-routine study-related procedures; the document contains all the essential elements of consent and has been previously approved by the sponsor and IEC. Reference of written informed consent will be provided in source documentation
- Submission of any protocol amendment to the IEC. If the protocol amendment change(s) increase risk to the study population, full IEC written approval must be obtained prior to implementation. For changes that do not involve increased risk or affect the validity of the investigation or the patient's rights, prior IEC approval may be obtained by expedited review
- Adherence to the study protocol. Documentation and explanation of individual post-enrolment protocol deviations will be recorded in the source documentation at the site and be provided to Panoptes Pharma GesmbH
- Notification to Panoptes Pharma GesmbH of all serious adverse events (SAEs), regardless of relationship to study drug, as specified in the protocol. Notification to the IEC of SAEs as specified in the protocol and per additional guidelines as provided by the IEC

- Notification to IEC of all unanticipated problems within the timeframe provided by the IEC. For the purposes of this study, unanticipated problems are defined as any incident, experience, or patient outcome that meets **all** of the following criteria: (1) unexpected; (2) related or possibly related to participation in the study; (3) and suggests that the research places patients or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known
- Provision of adequate study oversight by personally conducting or supervising the investigation, including, but not limited to: allotting sufficient time to properly conduct and complete the study within the agreed upon time period; having available an adequate number of qualified staff and adequate facilities for the expected duration of the study and to conduct the study properly and safely; and ensuring that all persons assisting with the study are adequately informed about the protocol and the investigational product(s) and are capable of performing their study-related duties and functions. Qualifications of individuals assigned responsibility for the administration of the investigational product will be compliant with state and local law or national regulations, as applicable
- Submission of timely progress reports to the IEC and Panoptes Pharma GesmbH at appropriate intervals not to exceed 1 year and submission of a final report to the IEC within the timeframe set by the IEC, but not later than 3 months after the completion or termination of the clinical investigation
- Maintenance of accurate source records from which case report forms are completed as well as drug accountability records that show the receipt and disposition (on an overall and per patient basis) of all study drug(s) shipped to the Investigator by Panoptes Pharma GesmbH

In addition, I agree to provide all the information requested in the electronic case report form (eCRF) presented to me by Panoptes Pharma GesmbH by carefully following the completion guidelines provided as part of the eCRF.

If I opt to terminate my participation in the study, the foregoing shall equally apply.

Prof. Dr. Stephan Thurau

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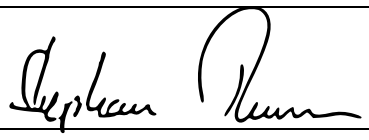

Investigator's Signature

SYNOPSIS

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

Study Objectives:

Primary Objective

- To assess the safety and tolerability of ascending doses of PP-001 in patients with chronic, non-infectious uveitis when administered as a single intravitreal injection of 0.3 µg, 0.6 µg and 1.2 µg with the option of an addition cohort with a dose of 2.1 µg PP-001

Secondary Objectives

- To assess the improvement of inflammation in patients with chronic, non-infectious uveitis after ascending doses of PP-001 when administered as a single intravitreal injection of 0.3 µg, 0.6 µg and 1.2 µg with the option of an addition cohort with a dose of 2.1 µg PP-001
- To evaluate the pharmacokinetics of PP-001 in patients with chronic, non-infectious uveitis when administered as a single intravitreal injection of 0.3 µg, 0.6 µg and 1.2 µg with the option of an addition cohort with a dose of 2.1 µg PP-001

Study Population:

Inclusion Criteria

1. Male or female patients without childbearing potential older than 18 years of age 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 and patients must not have a diagnosis of any acute or chronic illness except uveitis.
3. A signed and dated written informed consent form.
4. A signed and dated written data protection consent form.
5. Male 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 fathering a child in the 3 months following the last study drug administration. Male patients 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. Female patients must be of non-childbearing potential. The definition of non-childbearing potential includes the following:
    - Surgically sterile (e.g., hysterectomy with or without oophorectomy; fallopian tube ligation; endometrial ablation), at least 30 days prior to signature of the Informed Consent form
    - At least 3 years post-menopause (i.e., 4 years post last menstrual period), or menopause confirmed by follicle-stimulating hormone (FSH) testing.

6. 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.
7. Have chronic, posterior uveitis, intermediate uveitis or panuveitis requiring treatment
8. Have media clarity, pupillary dilation and patient cooperation sufficient for adequate visualization of the optic nerve in the study eye.
9. 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.*
10. 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 50 letters (approximately 20/100 or 0.2) in the study eye.
11. Best-corrected ETDRS visual acuity of 50 letters or better in the fellow eye (approximately 20/100 or 0.2)

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 of childbearing potential or who are pregnant.
20. Use of any anticoagulant or thrombocyte aggregation inhibiting agent (marcumar, warfarin, heparin, enoxaparin, apixaban, rivaroxaban, pentosanpolysulfate, dabigatran, aspirin, and others) less than 14 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).
22. Patients with diagnosis of any acute or chronic systemic illness other than uveitis

Duration of Study: Total duration of study for each patient will be 8 weeks or less (from screening to last follow-up).

Drug Products: PP-001 will be supplied as a sterile concentrate solution in a 2 ml vial and will be diluted according to dose as specified in the pharmacy manual.

Study Drug Assignment: Patients will be dosed in ascending order with 0.3, 0.6, 1.2 or 2.1 µg PP-001 depending on the cohort to which they are assigned.

Duration of Treatment: Patients will receive a single dose of PP-001.

Study Drug Administration: PP-001 will be administered as a single intravitreal injection, which will be performed under sterile conditions in an operating room setting. 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 not 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.

Blinding: This is an open-label study.

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 older than 18 years of age 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 50 letters (approximately 20/100 or 0.2) in the study eye.

The study will involve eight inpatient visits (Screening, Baseline, the day of injection [Day 0] and Days 2, 7, 14, 21 and 28) and telephone calls on Day 1 and on Day 40.

Patients will be divided into three cohorts of four patients. Patients 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 start of injection of the previous patient and start of injection of the next patient. The results from each dosing day will be reviewed before progressing with the subsequent dosing day. The next cohort will only commence with dosing after the previous cohort has completed all study sessions up to Day 28 and no safety issues have been identified after being 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.

Statistical Considerations:

- Sample Size: Eighteen patients will be enrolled in the study. No power calculations will be performed and the sample size is based on the requirements of the study design.
- Treatment Comparison of Interest: a comparison will be made between the cohorts with regard to safety tolerability and efficacy.

Interim Analysis: the results from each dosing day of the first cohort will be reviewed before progressing with the subsequent dosing day. Dosing of the next cohort will only commence after the previous cohort has completed all study sessions up to Day 28 and no safety issues have been identified after being reviewed by the SDMB.

Analysis Populations

- *Intent-to-treat (ITT) Analysis Set*: all patients regardless of whether or not the patient received study drug
- *Per-protocol Analysis Set*: all ITT Analysis Set patients who have no major protocol deviations, and who complete the study up to the end of the post-study assessments
- *Safety Analysis Set:* all patients who receive any amount of study drug. All safety analyses will be conducted in this population

- *Pharmacokinetic Analysis Set:* all patients who receive any amount of study drug will be included in the formal analysis of pharmacokinetic parameters providing they have at least one evaluable pharmacokinetic sample

Variables for Analysis:

Primary

- Safety parameters (i.e., changes in clinical signs and symptoms from ophthalmic exam, and AEs)

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

Safety analysis

The incidence of treatment-emergent adverse events (TEAEs), SAEs, deaths and discontinuations of study drug due to an AE or SAE will be summarized by System Organ Class and Preferred Term according to the Medical Dictionary for Regulatory Activities, by relationship to study drug, and by severity. The incidence of potentially clinically significant vital signs will be summarized.

Pharmacokinetic analysis

The concentration of PP-001 in plasma will be measured in blood samples taken at Screening, 4 h ± 1 h after dosing and on Day 2.

Table 1. Schedule of Assessments and Procedures

Phase	**Screening**	**Baselinei [i]**	**Pre injection**	**Post injection**	**Telephone call[a]**	**Safety visits**					**Telephone call[a]**
Day	-14 up to dosing	-7 up to dosing	0	0	1	2	7 *+/-1*	14 *+/-1*	21 *+/-1*	28[h] *+/-1*	40
Electroretinography		X						X		X	
Fluorescein angiogram	X									X	
Optical coherence tomography		X				X	X	X	X	X	
Best corrected visual acuity (ETDRS)	X	X				X	X	X	X	X	
Visual field (computerized, 30°)		X					X			X	
Visually evoked cortical potential	X									X	
Intraocular pressure	X	X		X[b]		X	X	X	X	X	
Slit lamp examination [c]	X	X	X	X[b]		X	X	X	X	X	
Dilated fundoscopy[d]	X	X		X[b]		X	X	X	X	X	
Study drug injection				X							
Blood sampling for PK analysis	X			X[b,e]		X					
Corneal endothelial microscopy		X					X			X	
Fundus photography		X								X	
Amsler grid		X				X	X	X	X	X	
Medical and ophthalmic histories	X	X									
Vital signs[f]	X	X	X			X	X	X	X	X	
Twelve-lead electrocardiogram	X									X	
Laboratory assessments	X									X	
Patient-reported outcomes[g]		X								X	
Concomitant medication	X	X	X		X	X	X	X	X	X	
Serious medical events	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X

ETDRS: Early Treatment of Diabetic Retinopathy Study; PK: Pharmacokinetic

a. Standardized questions including (but not limited to): pain, blurred vision, change in visual acuity, redness of the eye

b. Examination will be performed after administration of study drug

c. Conjuctiva, cornea, anterior chamber including grading of cells and haze (Standardization of Uveitis Nomenclature Working Group), lens (Lens opacities classification system II) and vitreal haze (Standardization of Uveitis Nomenclature Working Group)

d. Including slit lamp biomicroscopy of the fundus

e. Day 0 blood sample will be taken 4 h ± 1 h after injection

f. Blood pressure and heart rate

g. National Eye Institute Visual Functioning Questionnaire 25 (VFQ-25), SF36™ Health Survey Version 2 (SF-36v2) and EuroQol-5 Dimensions Health Questionnaire (EQ-5D)

h: for visit 28 option to perform examinations to 2 consecutive days;

i: 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

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse event
AUC	Area under the plasma concentration time curve
BP	Blood pressure
CS	Clinically significant
C_{max}	Maximum plasma concentration
DHODH	Dihydroorotate dehydrogenase
EAU	Experimental autoimmune uveitis
ECG	Electrocardiogram
eCRF	Electronic case report form
ETDRS	Early Treatment of Diabetic Retinopathy Study
EU	European Union
GCP	Good clinical practice
GLP	Good laboratory practice
h	Hours
hERG	Human ether-à-go-go-related gene
HR	Heart rate
IC_{50}	Half-maximal inhibitory concentration
ICH	International Conference on Harmonization
IEC	Independent ethics committee
ITT	Intent-to-treat
IFN-γ	Interferon gamma
IL-17	Interleukin 17
IOP	Intraocular pressure
K_3EDTA	Tri-potassium ethylenediaminetetraacetic acid
MedDRA	Medical Dictionary for Regulatory Activities
NCS	Not clinically significant
NIU	Non-infectious uveitis
NOAEL	No-observed-adverse-effect-level
NOEL	No-observed-effect level
OCT	Optical coherence tomography
OECD	Organisation for Economic Co-operation and Development
PP	Per-protocol
QA	Quality assurance
SAE	Serious adverse event
SDMB	Safety data management board
TEAE	Treatment-emergent adverse event
TNF	Tumour necrosis factor

TABLE OF CONTENTS

1. INTRODUCTION

1.1 Background of the Disease and Treatment Options

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 [Barisani-Asenbauer et al., 2012; Barry et al., 2014].

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 [Caspi, 2008]. 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 [Barry et al., 2014]).

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.

In NIU, T-cells (Th1 and Th17) become autoreactive towards ocular antigens like retinal-soluble antigen or interphotoreceptor retinoid-binding protein and this leads to a substantial immune response. Once activated, T helper cells secrete many different cytokines, of which interferon gamma (IFN-γ) and interleukin 17 (IL-17) are the hallmarks of Th1 and Th17 cells, respectively. This results in the recruitment of neutrophils and other leukocytes as well as lymphocytes from the peripheral blood to the eye. Subsequent tissue destruction is mediated by non-specific activation of immune cells.

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 [Barry et al., 2014]. 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.

1.2 Background on PP-001

PP-001 has the molecular formula $C_{19}H_8F_7NO_4S$ and a molecular weight of 479.3 g/mol. PP-001 is a third generation small molecule inhibitor of dihydroorotate dehydrogenase (DHODH) and has a half-maximal inhibitory concentration (IC_{50}) of DHODH of less than 4 nM. By inhibiting

DHODH, the expression of IL-17 and IFN-γ is suppressed. Independently, highly proliferating T cells are inhibited. PP-001 thereby specifically targets the underlying cause of uveitis.

PP-001 is 150-fold more potent than the orally administered small-molecule DHOHD inhibitor, leflunomide (IC_{50} DHODH, 650 nM). Leflunomide (Arava®) and its active metabolite teroflunomide (Aubagio®) are approved for the treatment of rheumatoid arthritis and multiple sclerosis, respectively. PP-001 is structurally and mechanistically distinct from leflunomide. The hepatic metabolization of leflunomide to teriflunomide leads to the off-target inhibition of protein kinases and is responsible for its side effect profile [Herrmann et al., 2000].

PP-001 drug substance is a small, synthetic molecule. The drug product is formulated as 1 mg/ml sterile concentrate formulation in 2 ml glass vials (PP-001 concentrate for intravitreal injection). Buffer and tonicity agents are added as excipients. Prior to administration, the PP-001 concentrate solution is diluted with sterile aqueous sucrose solution to the final dosing solution (PP-001 solution for intravitreal injection).

1.3 Non-Clinical Development

1.3.1 Mechanism of Action and Non-Clinical Pharmacology

Proof of concept for PP-001 in the treatment of non-infectious uveitis was established in a rat experimental autoimmune uveitis (EAU) model following oral and intravitreal administration of PP-001. In these studies, PP-001 was shown to be effective in prevention and treatment of experimentally induced autoimmune uveitis. Treatment with PP-001 at an oral dose level of 25 mg/kg significantly reduced the number of relapses and their intensity when compared to control. The determined ocular exposures (AUC) at the oral efficacious dose level of 25 mg/kg in rat were 1.27 µg·h/g and 4.8 µg·h/g for vitreous and retina, respectively. Intravitreally dosed PP-001 (3 µg/eye) reduced the number of relapses per eye by 50% when compared to control.

Inhibition of the human ether-à-go-go-related gene (hERG) channel by PP-001 was not indicated when tested at concentrations well above the intended human exposure. The 14-day intravenous repeated dose toxicity study in rats did not show evidence for adverse effects on safety pharmacology parameter at the highest dose tested (1 mg/kg body weight). PP-001 is intended for intravitreal use with no need of systemic availability of the drug. The systemic exposure in humans is expected to be below the minimal biologically active concentration of 958 ng/ml for T-cells and 58–265 ng/ml for evaluated cytokines. Thus, no stand-alone *in vivo* safety pharmacology studies were conducted.

1.3.2 Pharmacokinetics and Product Metabolism

Pharmacokinetic and metabolic parameters have been evaluated in several *in vitro* and *in vivo* experiments in various species.

PP-001 exhibited strong *in vitro* plasma protein binding properties with bound fraction levels of >99.9%. PP-001 exhibited high metabolic stability after incubation with human liver microsomes. Inhibition potential towards human Cytochrome P450 enzymes was detected but considered insignificant due to low systemic PP-001 exposure after intravitreal administration.

Following intravitreal administration of 60 to 250 µg PP-001 per animal, systemic exposure in the low ng/ml range was detected. Systemic exposure at efficacious human doses (0.6–1 µg/eye) is expected to be even lower. The half-life of PP-001 after intravitreal injection in rabbits was between 12 and 21 hours in ocular tissues and between 5 and 6 hours in peripheral blood. PP-001 does not elicit ocular melanin binding properties as shown in an *in vivo* ocular distribution study that compared pigmented rats with albino rats.

1.3.3 Non-Clinical Safety and Toxicology

Non-clinical safety and toxicology studies included acute (intravitreal) and repeated dose (intravenous) toxicity testing in rabbits and rats, and *in vitro* genotoxicity testing in bacterial and mammalian cells. All pivotal non-clinical studies were conducted in a country that is a member of the Organisation for Economic Co-operation and Development (OECD) Mutual Acceptance of Data program in accordance with the OECD Test Guidelines and Principles of Good Laboratory Practice (GLP) and respective ICH and Committee for Medicinal Products for Human Use guidance.

When PP-001 was given via the systemic route the no-observed-effect level (NOEL) in a 14-day repeated dose toxicity study in rats was 1 mg/kg body weight, which was the highest dose tested. In this study, the detected systemic exposure was several hundred fold higher than the expected exposures after intravitreal therapeutic doses in humans and thus provides an adequate safety margin with respect to systemic toxicity.

In an ocular extended single dose toxicity study conducted in rabbits (12 eyes dosed in 6 animals), intravitreal injection of PP-001 was shown to be safe with a no-observed-adverse-effect-level (NOAEL) of 10 µg/eye over an observation period of 15 days. Higher doses (20 and 30 µg/eye) resulted in adverse changes in retina (retina detachment and retinal tear, focal exudation etc.), choroid (vessel enlargement, choroidal exudates) and vitreous (floaters). There was no test item related intraocular pressure (IOP) abnormality or any other finding in body weight change, food and water consumption and clinical pathology in any dose group observed during the course of the study. Toxicokinetic analysis of blood plasma after dosing with 30 µg in each eye established that maximum plasma concentration (43.5 ng/ml) was reached at 4 h post dosing and PP-001 was not detectable after 8 h post dosing. There was no test item related intraocular pressure (IOP) abnormality or any other finding in body weight change, food and water consumption and clinical pathology in any dose group observed during the course of the study

PP-001 did not show genotoxic potential in *S. typhimurium* tester strains and a mouse lymphoma assay. No phototoxic risk is indicated since PP-001 does not absorb light at relevant wavelengths.

1.4 Summary of Clinical Data

This is a first time in human study therefore no clinical data is available.

2. STUDY OBJECTIVES

Primary Objective

- To assess the safety and tolerability of ascending doses of PP-001 in patients with chronic, non-infectious uveitis when administered as a single intravitreal injection of 0.3 µg, 0.6 µg and 1.2 µg with the option of an addition cohort with a dose of 2.1 µg PP-001

Secondary Objectives

- To assess the improvement of inflammation in patients with chronic, non-infectious uveitis after ascending doses of PP-001 when administered as a single intravitreal injection of 0.3 µg, 0.6 µg and 1.2 µg with the option of an addition cohort with a dose of 2.1 µg PP-001
- To evaluate the pharmacokinetics of PP-001 in patients with chronic, non-infectious uveitis when administered as a single intravitreal injection of 0.3 µg, 0.6 µg and 1.2 µg with the option of an addition cohort with a dose of 2.1 µg PP-001

2.1 Primary Endpoints

- Safety parameters (i.e., changes in clinical signs and symptoms from ophthalmic exam, and AEs)

2.2 Secondary Endpoint

- 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

3. 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 older than 18 years of age 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 50 letters (approximately 20/100 or 0.2) in the study eye.

Patients must give written consent for the study before any study assessments are performed. Screening assessments will be performed 8–14 days before dosing. Baseline assessments will be performed no more than 7 days before injection. The study will involve eight study visits (Screening, Baseline, the day of injection (Day 0) and Days 2, 7, 14, 21 and 28) and telephone calls on Day 1 and Day 40.

Patients will be divided into three cohorts of four patients. Patients 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.

An overview of the schedule of assessments/procedures is presented in Table 1.

3.1 Study Rationale

PP-001 is proposed for development as an intravitreal injection for the treatment of NIU. This first time in human study will investigate the safety, tolerability and efficacy of single ascending doses of PP-001 using intravitreal injection in male and female patients. The study population will comprise patients with NIU and an otherwise good state of health to ensure homogeneity.

Patients with chronic posterior uveitis, intermediate uveitis or panuveitis, for whom maximal medical treatment failed or who are unable to tolerate medical treatment because of adverse ocular or systemic effects will be included in this study. The data generated in this study will

support the progression of a well-tolerated dose of PP-001, administered by intravitreal injection in patients with NIU.

3.1.1 Dose Rationale

PP-001 will be developed for the treatment of non-infectious posterior uveitis.

For evaluation of a safe human starting dose, a calculation based on a mg/kg basis is not considered appropriate for intravitreally administered drugs. However, in the EU there is no applicable guidance available in this regard and thus, reference is made to the Food and Drug Administration's *Note for Guidance Estimating the Maximum Safe Starting Dose in Initial Clinical Trials* [Food and Drug Administration, 2005]. For PP-001, the starting dose was evaluated by normalization the compartmental volumes and concentrations of the therapeutic doses between rabbits and humans. Using the different volumes for vitreous humour (rabbit and human) the NOAEL dose of 10 µg/eye in rabbits would therefore correspond to a human dose of 26.7 µg/eye.

Since this study will involve patients data on the minimum efficacious dose of PP-001 and its exposure in vitreous and retinal tissues (which are both considered the main target tissues) are considered. More importantly, this calculation provides an additional safety margin compared to a simple normalization based on differences in the size of eyes (rabbit vs. human) and is to be preferred because of the steep dose-toxicity curve that was observed in the intravitreal toxicity study in rabbits.

An oral dose of 25 mg/kg was shown to be efficacious in the EAU rat model. This dose level led to an ocular AUC of 1.27 µg·h/g and 4.8 µg·h/g for vitreous and retina in pigmented animals, respectively. Exposure of vitreous and retina have been determined after intravitreal injection of various doses of PP-001 into pigmented rabbit eyes. By applying a linear extrapolation it was calculated that an efficacious dose of approximately 0.25–0.36 µg/eye in rabbits corresponds to an efficacious retinal AUC of 4.8 µg·h/g, whereas a dose of 0.20–0.27 µg per rabbit eye is needed to reach an efficacious vitreous AUC of 1.27 µg·h/g (see Table 2).

Considering the higher vitreous volume of the human eye, a dose of 0.54 to 0.96 µg/eye is expected to achieve efficacious exposure in the human vitreous and retina, respectively.

Table 2 Calculated Human Efficacious Exposure and Dose

Species	Vitreous humour [ml]	Efficacious dose based on exposure in retina	Efficacious retinal AUC (µg·h/g)	Efficacious dose based on vitreous Exposure	Efficacious vitreous AUC (µg·h/g)
Rat	0.056	25 mg/kg		25 mg/kg	
Rabbit	1.5	0.25–0.36* µg/eye	4.8	0.20–0.27* µg/eye	1.27
Human	4	0.67–0.96** µg/eye		0.54–0.73** µg/eye	

AUC: Area under the plasma concentration time curve

* Calculated efficacious dose based on PK study in rabbits; values are calculated by dividing the applied intravitreal dose/eye by obtained the AUC from time 0 to time t in pigmented rabbits (see Section 1.3.2) multiplied by the efficacious AUC in pigmented rats (see Section 1.3.2); ** Calculated efficacious human dose using the vitreous volume difference between rabbit and human.

It must be noted that the calculation above is only an estimation. Due to inter-individual variations in the volume of vitreous humour, an even lower starting dose of 0.3 µg/eye is proposed for this first time in human study.

With a starting dose of 0.3 µg/eye an appropriate safety margin of 86 is provided as depicted below in Table 3.

Table 3 Safety Margin Calculation of Human Starting Dose

Species	Vitreous Humour [ml]	Dose [µg/eye/patient]	Proposed Starting Dose [µg/eye/patient]	Safety Margin*
Rabbit	1.5	10		
Human	4	26.7*	0.3	>86**

* Calculated human equivalent dose based on normalization of compartment volumes of the vitreous.
** Safety margin to calculated human equivalent dose.

In conclusion, the proposed starting dose of 0.3 µg/eye provides an adequate safety margin for clinical study PP-001-1001 with respect to local and systemic toxicity. Plasma levels following a single intravitreal dose of 0.3 µg/eye will lead to a negligibly low plasma exposure of PP-001 (if present at all) and thus no systemic toxicity is expected. Regarding local effects observed in the eye the starting dose provides a safety margin >86-fold compared to the calculated human equivalent dose derived from an extended single dose study in rabbits, where 10 µg/eye was considered to be the NOAEL.

Consecutive dosing and careful monitoring using state of the art methodology will provide additional safety level.

3.2 Potential Risks and Benefits to Human Patients

PP-001 is a novel chemical molecule to inhibit a known enzyme called DHODH, a known drug target for systemic treatment of rheumatoid arthritis, psoriatic arthritis and multiple sclerosis. PP-001 is a novel inhibitor of DHODH and has the potential to deliver a new treatment for patients with severe non-infectious uveitis. Currently patients suffering from intermediate and/or the posterior uveitis (i.e., the vitreous body and retina/choroid are affected) are routinely treated with systemic corticosteroids with well known side effects. The future expected therapeutic role of PP-001 will be as a steroid-sparing agent that will allow steroid doses to be tapered quickly or even replaced.

In this proposed study the safety and tolerability of single doses of intravitreally administered PP-001 will be evaluated. Based on the preclinical pharmacokinetics the ocular half-life is

expected to be less than 20 h and the systemic exposure is expected to be below the biological activity and close to or below the limit of detection of the applied bioanalytical method (10 ng/ml). Due to the local treatment (intravitreal injection) and the preclinical data on plasma exposure of PP-001 it is unlikely that there will be any systemic exposure of PP-001 in human and therefore no systemic effects of PP-001 are expected.

This study will identify the tolerated doses at expected efficacious ocular exposures and will serve as the basis for further studies long term acting PP-001.

The inclusion and exclusion criteria restrict access to the study to severely affected patients with severely compromised visual acuity

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.

4. STUDY POPULATION

4.1 Inclusion Criteria

1. Male or female patients of non child bearing potential older than 18years of age who have diagnosis of chronic posterior uveitis, intermediate uveitis or panuveitis.
2. Good state of health (mentally and physically). Laboratory parameters and vital signs of patients must be within the normal ranges and patients must not have a diagnosis of any acute or chronic illness except uveitis.
3. A signed and dated written informed consent form.
4. A signed and dated written data protection consent form.

5. Male 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 fathering a child in the 3 months following the last study drug administration. Male patients 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. Female patients must be of non-childbearing potential. The definition of non-childbearing potential includes the following:
    - Surgically sterile (e.g., hysterectomy with or without oophorectomy; fallopian tube ligation; endometrial ablation), at least 30 days prior to signature of the Informed Consent form
    - At least 3 years post-menopause (i.e., 4 years post last menstrual period), or menopause confirmed by follicle-stimulating hormone (FSH) testing.
6. Have diagnosis of chronic posterior uveitis, intermediate uveitis or panuveitis (as defined by the Standardization of Uveitis Nomenclature Working Group 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.
7. Have chronic uveitis, posterior, intermediate uveitis or panuveitis requiring treatment.
8. Have media clarity, pupillary dilation and patient cooperation sufficient for adequate visualization of the optic nerve in the study eye.
9. 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.
10. 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 50 letters (approximately 20/100 or 0.2) in the study eye.
11. Best-corrected ETDRS visual acuity of 50 letters or better in the fellow eye (approximately 20/100 or 0.2).

4.2 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.
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 ≥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 of childbearing potential or who are pregnant.
20. Use of any anticoagulant or thrombocyte aggregation inhibiting agent (marcumar, warfarin, heparin, enoxaparin, apixaban, rivaroxaban, pentosanpolysulfate, dabigatran, aspirin and others) less than 14 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 and povidone).
22. Patients with diagnosis of any acute or chronic systemic illness other than uveitis.

5. STUDY DRUG ADMINISTRATION

See Section 8 for a complete description of study drugs. Instructions for the preparation of the study drugs will be provided in a Pharmacy Manual.

5.1 Randomization

This is a non-randomized study. Patients will be assigned to the next available cohort as they are recruited to the study.

5.2 Study Drug Treatment

5.2.1 Duration of Treatment

Patients will receive a single intraocular dose of PP-001.

5.2.2 Post-Baseline Treatment Modifications

The results from each dosing day will be reviewed before progressing with the subsequent dosing day. Dosing in the next cohort will only commence with dosing after the previous cohort has completed all study sessions up to day 28 and no safety issues have been identified after being reviewed by the SDMB.

5.3 Timing of Dosing and Dose Administration

The study drug will be administered on Day 0 following the completion of all pre-dose procedures.

5.4 Preparation of Treatment

A Pharmacy Manual will be provided to investigative sites with additional details on preparation of study drug material.

5.5 Blinding

This is an open-label study.

5.6 Unblinding of Therapy Assignments

As this is an open-label study, unblinding will not be required.

5.7 Adherence

Throughout the study, hospital staff or study personnel will administer all doses of study drug. The date, start and stop time of each dose will be recorded in the electronic case report form (eCRF).

5.8 Occupational Safety

PP-001 is not expected to pose any occupational safety risk to site staff under normal conditions of use and administration.

A Material Safety Data Sheet describing occupational hazards and recommended handling precautions either will be provided to the Investigator, where this is required by local laws, or is available upon request from Panoptes Pharma GesmbH.

In line with good handling of chemical products, precautions are to be taken to avoid skin and eye contact. In the case of unintentional occupational exposure, any signs or symptoms should be treated appropriately and the Sponsor notified.

6. STUDY ASSESSMENTS AND PROCEDURE

A schedule of study procedures is presented in Table 1. Patients meeting the eligibility criteria listed in Section 4 may be enrolled in the study after the nature and purpose of the protocol have

been explained and written informed consent to participate has been voluntarily given. Study personnel must complete all screening procedures after informed consent is signed and before the first dose of study drug. Note: assessments performed as part of routine standard of care before consent may be used to satisfy study screening requirements; however, no study-specific procedures may be performed before informed consent is given.

The time and day on which PP-001 is administered will be regarded as 0 h on Day 0. The Investigator should make every effort to perform procedures at the scheduled times and to record the actual time of the procedures, where appropriate, in the patient's eCRF.

For patients who are screened (i.e., those with signed written informed consent) but do not meet the screening criteria, the reason for screening failure will be recorded.

6.1 Surgical Procedure

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 (see Section 8). 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.

6.2 Medical/Surgical History

A medical and surgical history will be taken at Screening. All medical history findings that have been present/active within 5 years before enrolment will be entered into the eCRF regardless of clinical relevance or presence at study start. Medical history findings that have not been present within the 5 years before enrolment will be recorded if deemed clinically relevant to the conduct of the study by the Investigator. The medical history should include drug allergy history and past and present smoking status.

6.3 Physical Examination

A complete physical examination will be performed by the Investigator at Screening. At the time points specified in Table 1, subsequent directed physical examinations will be performed according to standard institutional practices and must be documented in source documents.

Body weight and height will be measured at Screening only.

6.4 Vital Signs

Vital signs (heart rate [HR] and blood pressure [BP]) will be recorded at time points specified in Table 1. Blood pressure and HR will be assessed according to standard practice at the clinical sites. Study personnel will record vital sign measurements in the eCRF.

Vital signs measurements are to be repeated if clinically significant changes or machine errors occur. Out of range BP and HR will be repeated at the Investigator's discretion. Semi-supine BP and HR will be measured more frequently if warranted by the clinical condition of the patient.

6.5 Twelve-Lead Electrocardiogram

Triplicate 12-lead electrocardiograms (ECGs) will be performed within a 5-minute interval at the time points outlined in Table 1.

The patient should be stabilized in a supine position for 5 minutes before recording the ECG at Screening. The ECG recordings should allow a full assessment of QT intervals. Machine-read values for QTc/QTcF will be evaluated for determination of eligibility at Screening. If the quality of the ECG is insufficient then it must be repeated. All ECG data must be reviewed by the attending physician and any findings of clinical significance found following Screening will be recorded as AEs in the eCRF. In addition, advice may be sought from appropriate cardiologists, if necessary. All ECGs will be made available to the Sponsor for review and might be sent to a Cardiac Core Laboratory for further evaluation.

6.6 Clinical Laboratory Tests

Safety laboratory tests will be performed at the time points specified in Table 1 and sent to a local laboratory. Additional tests may be performed at the discretion of the Investigator if deemed clinically appropriate. If required, samples may be sent to a central laboratory for confirmation of local results.

A full list of the clinical laboratory tests that will be performed and analyzed is presented in Section 21.1.

Any safety laboratory results outside the normal range will be repeated at the discretion of the Investigator and will be evaluated by the Investigator or designee as "clinically significant (CS)" or "not clinically significant (NCS)." Any CS value should be repeated as necessary and followed until resolution.

6.7 Opthalmic Examination Procedures

Detailed ophthalmic examination will be used to evaluate screening criteria, determine efficacy and as a safety measure. All procedures should be performed at the times outlined in Table 1. The primary efficacy variable is vitreous haze. The ophthalmologist will grade vitreous haze by viewing the optic disc and posterior retina using an indirect ophthalmoscope set to large beam and mid power illumination with a 20-diopter lens. Low ambient lighting and the same indirect ophthalmoscope should be used whenever possible. The scale is based on the following unit scale categorized as follows:

0	No inflammation
+0.5	Trace inflammation (slight blurring of the optic disc margins and/or loss of the NFL reflex)
+1	Mild blurring of retinal vessels and optic nerve

+1.5	Optic nerve head and posterior retinal view obscuration greater than +1, but less than +2
+2	Moderate blurring of optic nerve head
+3	Marked blurring of optic nerve head
+4	Optic nerve head not visible

6.7.1 Electroretinography

Patients will receive anaesthetic drops and the patient's eyelids will be kept open with a speculum. An electrode is gently placed on each eye and an additional electrode is placed on the skin to provide a ground. Electrical signals produced by the retina in response to light will be measured with the electrodes.

6.7.2 Fluorescein Angiogram

Fluoroscein angiograms will be used to assess blood flow in the retina and choroid. Dilation eye drops will be given to patients, who will then place their chin on a chin rest and forehead against a support bar. Images of the retina, papilla, macular region and the choroid will be taken.

6.7.3 Optical Coherence Tomography

Three-dimensional images of the eye will be generated using optical coherence tomography (OCT). OTC is a laser-based, non-invasive, diagnostic system providing high-resolution images of the retina and retinal thickness. Optical coherence tomography will be performed in the study eye only. High-resolution cross-sectional images will be examined for physiological abnormalities.

6.7.4 Best Corrected Visual Acuity

Best corrected visual acuity will be measured in both eyes using an ETDRS chart. Patients will be asked to read the smallest letters they can from a chart.

6.7.5 Visual Field Measurement

Computerised 30° visual field measurement will be conducted.

6.7.6 Visually Evoked Cortical Potential

The electrical response of the primary visual cortex to a visual stimulus will be measured. Three electrodes will be placed on the scalp. One electrode will measure the response, another electrode will be placed at a reference location, typically on the forehead or top of the head. The third electrode will be placed on the patient's ear for grounding. These electrodes will be connected to a visual electrodiagnostic test system.

6.7.7 Intraocular Pressure

Intraocular pressure will be measured using Goldman contact tonometry.

6.7.8 Slit Lamp Examination

A slit lamp will be used to examine the conjuctiva, cornea, anterior chamber including grading of cells and haze (classified according to Standardization of Uveitis Nomenclature Working Group criteria), lens (classified according to Lens opacities classification system II) and vitreal haze (classified according to Standardization of Uveitis Nomenclature Working Group).

6.7.9 Dilated Fundoscopy

Visualization of the fundus will be carried out as part of an eye exam by dilating the patient's pupils. This procedure will include slit lamp biomicroscopy of the fundus.

6.7.10 Corneal endothelial microscopy

The corneal endothelial layer will be assessed by microscopic evaluation of the cornea.

6.7.11 Fundus photography

The eye, retina, retinal vasculature, optic disc, macula and posterior pole will be photographed using a retinal camera. Vitreous haze will also be documented.

6.7.12 Amsler grid

To test for macular degeneration, patients will be asked to look at an Amsler grid and wear their reading glasses. With one eye covered, patients will be asked to state if any of the lines appear wavy, blurred or distorted, whether there are missing or dark areas in the grid. The test will be repeated for both eyes.

6.7.13 Health Outcome Measures

Patient-reported outcomes will be assessed using the National Eye Institute Visual Functioning Questionnaire 25 (VFQ-25), SF36™ Health Survey Version 2 (SF-36v2) and EuroQol-5 Dimensions Health Questionnaire (EQ-5D). For additional information on these outcome measures, refer to the Procedure Manual.

6.8 Telephone Interview

A telephone interview will take place on Day 1 to evaluate the safety of PP-001. Standardized questions will be used and will include (but not be limited to) assessment of pain, blurred vision, change in visual acuity and eye redness.

6.9 Prior and Concomitant Medications

Prior and concomitant medications that will be recorded include prescription medications, dietary supplements/vitamins and over-the-counter medications. Topical medications will be recorded only if used as treatment for an AE. The minimum requirement is that drug name, indication and the start and stop dates of administration are to be recorded.

6.9.1 Prior Medications

A medication history will be taken at Screening. All medications taken within 1 week before Day 0 will be entered into the eCRF.

6.9.2 Concomitant Medication

All concomitant medications taken during the study will be recorded in the patient's eCRF.

6.10 Prohibited Medications

The following medications are prohibited:

- Local biologicals
- Cyclophosphamide or chlorambucil
- Immunosuppressive, immunomodulatory or steroid treatment for any other disease than uveitis
- Any anticoagulant or thrombocyte aggregation inhibiting agent (marcumar, warfarin, heparin, enoxaparin, apixaban, rivaroxaban, pentosanpolysulfate, dabigatran, aspirin and others)
- Any systemic antibiotic treatment

6.11 Non-Pharmacologic Treatments and Procedures

Non-pharmacologic treatments and procedures (e.g., diagnostic) that occur during the study will be entered into the eCRF, including the date and reason for the treatment/procedure.

6.12 Sample Collection for Pharmacokinetic Analysis

6.12.1 Plasma Sample Collection

Blood samples for pharmacokinetic analysis of PP-001 in plasma following intraocular dosing will be collected at Screening, 4 h ± 1 h after dosing and on Day 2.

Blood samples will be collected from a vein in the opposite arm from the arm in which infusion is given into tubes containing K_3EDTA, as a coating, and immediately chilled on crushed ice. Plasma will be separated by centrifugation at approximately 2,000*g* for approximately 10 minutes at approximately +4 °C and transferred in equal aliquots (at least 300 µl) to 3 polypropylene screw top cryo vials labeled with the following: PP-001-1001, subject number,

date of dosing, nominal sampling time, aliquot ID (e.g. A, B, C). Promptly following centrifugation, plasma specimens will be immediately frozen and stored at approximately -20 °C or cooler until transported for analysis. The total time period from blood withdrawal to storage of plasma at approximately -20 °C should not exceed 60 minutes. The primary samples (aliquot A) should be transferred to the A&M analytical laboratory on dry ice.

6.12.2 Assay Methodology

Pharmacokinetic samples will be analyzed for the concentration of PP-001 using a validated liquid chromatography-tandem mass spectrometry method at the bioanalytical laboratory.

6.13 Total Blood Volume Collected

Patients will have approximately 20 mL of blood collected for safety and pharmacokinetic evaluations during the study.

6.14 Discontinuation from Treatment or Study

Patients are free to withdraw from the study at any time for any reason. Patients may be withdrawn from the study at the discretion of the Principal Investigator or Sub-Investigator at any time. Once a patient has been withdrawn from the study, they may not be re-entered. Patients who withdraw or who are withdrawn from the study will not be replaced. If a patient is discontinued from treatment or from the study, the reason for discontinuation will be collected in the eCRF.

If a patient is prematurely withdrawn from study drug treatment, the Investigator should make every effort to retain the patient in the study and perform all procedures scheduled for the follow-up. Any patient withdrawn from treatment due to an AE, serious AE (SAE) or clinically significant safety value will be evaluated by the Investigator, or a monitoring physician, and will be treated and/or followed up until the symptoms or values have either resolved or are assessed as stable by the Investigator.

6.14.1 Discontinuation from Study

A patient may be discontinued prematurely from the study for the following reasons:

- Withdrawal by patient (specify the reason in the eCRF)
- Lost to follow-up
- Death
- Physician decision (i.e., assessment that it is not in the patient's best interest to continue, or another reason; specify the reason in the eCRF)
- The sponsor may shut down the study at any time (specify the reason in the eCRF)

6.14.2 Individual Stopping Criteria

If an individual Patient meets one or more of the following criteria, the SDMB and Investigator will discuss whether the patient should be withdrawn from the study or dosing, or postponed until the criterion is no longer met:

- Patient develops a concurrent illness, condition or procedural complication that would interfere with the patient's continued participation
- Patient experiences a study drug-related SAE as determined by the Investigator

Patients may also be withdrawn from the study at any time at the discretion of the Investigator for other safety or tolerability reasons, or for behavioural or administrative reasons.

A patient may also withdraw from the study at any time at their own request.

If a patient is prematurely withdrawn from study treatment, the Investigator should make every effort to retain the patient in the study and to perform all procedures scheduled for the follow-up visit. Any patient withdrawn from treatment due to an AE, SAE or clinically significant abnormal laboratory test value will be evaluated by the Investigator, or a monitoring physician, and will be treated and/or followed up until the symptoms or values have either resolved or are assessed as stable by the Investigator.

6.14.3 Study Stopping Criteria

Dosing of further patients will be stopped if the following criterion is observed:

- A moderate or severe AE classified as being possibly, probably or definitively study-drug related or potential major safety concerns as identified by the Investigator after consultation with the SDMB are reported in more than 50% of patients in the same cohort.

Dosing will be stopped or the dose decreased if:

- One patient on any dosing day shows a possibly, probably or definitively study-drug-related SAE judged by the Investigator after consultation with the SDMB or other potential major safety concerns are identified by the Investigator in agreement with the SDMB.

6.14.4 Lost to Follow-up

If a patient does not report to the study site for a scheduled visit, study personnel will make four contact attempts: three telephone contact attempts and, if these are unsuccessful, a certified letter will be sent to the patient. The patient will be considered lost to follow-up if (1) upon receipt of delivery confirmation of the certified letter the patient does not contact the site or (2) the certified letter is returned as undeliverable within 7 days.

6.15 Premature Termination of the Trial

In the event of any SAE, which, in the investigator's opinion, justifies termination of the trial, dosing will be stopped and the sponsor will be informed immediately. The sponsor and

investigator reserve the right to terminate this trial should serious or severe AEs or any other safety issue occur during the trial. If the trial is terminated prematurely, the investigator will return all eCRFs to the sponsor, and the sponsor or investigator, as appropriate, will provide a written statement of the reasons for termination. The sponsor will ensure that the relevant regulatory agencies and main research ethics committees are notified.

6.16 Contraceptive measures

Female patients of childbearing potential are not allowed to participate in this study. The definition of non-childbearing potential includes the following:

- Surgically sterile (e.g., hysterectomy with or without oophorectomy; fallopian tube ligation; endometrial ablation), at least 30 days prior to signature of the Informed Consent form
- At least 3 years post-menopause (i.e., 4 years post last menstrual period), or menopause confirmed by follicle-stimulating hormone (FSH) testing.

Fertile men need to adhere to contraceptive measures in accordance with the "Recommendations related to contraception and pregnancy testing in clinical trials, September 2014" of the Clinical Trials Facilitation Group.

Male patients must ensure that one highly effective method of contraception 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 must refrain from fathering a child in the 3 months following the last study drug administration. Male patients 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.

Highly effective methods of birth control are defined as those that result in a low failure (i.e., < 1 % per year) when used consistently and correctly, such as:
- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
- progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
- intrauterine device
- intrauterine hormone-releasing system
- bilateral tubal occlusion
- vasectomised partner
- sexual abstinence

Acceptable birth control methods are defined as those that result in a failure rate of more than 1% per year and include:
- progestogen-only hormonal contraception, where inhibition of ovulation is not the primary mode of action
- male or female condom with or without spermicide
- cap, diaphragm or sponge with spermicide;

Periodic abstinence and withdrawal are not acceptable methods of contraception. Female partners of male patients must be informed by their male partners about the need to use one

highly effective methods of birth control combined with an acceptable method of birth control as defined above.

7. ADVERSE EVENTS

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational medicinal product.

Any pre-existing conditions or signs and/or symptoms present in a patient before the start of the study (i.e., before informed consent) should be recorded as medical/surgical history. Any medical occurrences that are new or worsened from the time of informed consent and up to and including the final visit must be reported as AEs or SAEs. All AEs and SAEs must be recorded irrespective of whether they are considered drug-related.

Patients will be monitored throughout the study for adverse reactions to the study medications and/or procedures at each study visit. Questions will be posed in a non-leading manner so as not to bias the response. In addition to questioning at specific time points, patients will be encouraged to report any AEs spontaneously. Any patient with an AE, SAE or clinically significant abnormal laboratory test value will be evaluated by the Investigator, or a monitoring physician, and will be treated and/or followed up until the symptoms or values have resolved or are assessed as stable by the Investigator. A physician, either at the Investigative site or at a nearby hospital emergency room, will administer treatment of any SAEs. Where appropriate, medical tests and examinations may be performed to ensure that an AE has fully resolved.

Adverse events will be monitored throughout the study from the time a patient is consented through the final follow-up visit; SAEs are to be collected from the time of consent through to the follow-up visit. Whenever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the patient's eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE on the patient's eCRF.

Each AE or SAE reported will be assessed for severity and the date and time of onset (if available), time relationship to dosing, duration and outcome of each event will be noted.

Laboratory abnormalities are not considered AEs unless they are associated with clinical signs and symptoms or require medical intervention. Clinically significant abnormal clinical laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the Investigator as more severe than expected for the patient’s condition, or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs.

The Investigator will exercise medical and scientific judgment in deciding whether an abnormal clinical laboratory finding or other abnormal assessment is clinically significant.

7.1 Assessment of Severity (Intensity)

The following definitions for rating severity (intensity) will be used:

Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but the patient is still able to function.

Severe: The type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

7.2 Assessment of Relationship to Study Drug

The Investigator will use his/her clinical judgment to explain each AE and determine its relationship, if any, to study drug treatment. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors and the temporal relationship of the event to the study drug will be considered and investigated. The Investigator will also consult the Investigator's Brochure in the determination of his/her assessment. Causality should be assessed using the following categories:

Not Related The event could readily be explained by factors not involving the study drug and a temporal relationship with the study drug did not exist.

Possibly Related There was some temporal relationship between the event and the administration of the study drug and the event was unlikely to be explained by the patient's medical condition or other therapies.

Probably Related The temporal relationship between the event and the administration of the study drug was suggestive, and the event was less likely to be explained by the patient's medical condition or other therapies.

Definitely Related The event followed a reasonable temporal sequence from administration of the study drug, followed a known or suspected response pattern to the study drug, was confirmed by improvement upon stopping the study drug (dechallenge) and reappeared upon repeated exposure (rechallenge). (Note: this is not to be construed as requiring re-exposure of the patient, however, a category of definitely related can only be used when recurrence was observed).

7.3 Serious Adverse Events

An SAE is any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Results in persistent or significant disability/incapacity

- Requires in patient hospitalization or prolongation of existing hospitalization
- Is a congenital anomaly/birth defect
- Is an important medical event

NOTE: medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of drug dependency or drug abuse.

All SAEs for patients occurring from the time of informed consent through to the follow-up visit must be reported to Panoptes Pharma GesmbH or their representative within 24 h of the knowledge of the occurrence (this refers to any AE that meets one or more of the aforementioned serious criteria). Reporting is done by completing the SAE form electronically in the eCRF system for the study.

The SAE form should be completed in as much detail as possible but a lack of complete information should not delay the reporting of the SAE.

There may be situations when an SAE has occurred and the Investigator has minimal information to include in the initial report to Panoptes Pharma GesmbH. However, it is very important that the Investigator always makes an assessment of causality for every event prior to transmission of the SAE report form to Panoptes Pharma GesmbH. The Investigator may change his/her opinion of causality in light of follow-up information, amending the SAE report form accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

The Investigator will provide the assessment of causality as per instructions on the SAE form in the CRF.

If an SAE occurs during this study, the following (Sponsor) personnel should be contacted:

Dr. Franz Obermayr:

Phone (office and after-hours): +43 664 8557369

7.4 Other Reportable Events

Certain events that occur in the absence of an AE should be reported to the Sponsor as Other

Reportable Events. These include the following:

- Pregnancy exposure (female partners of male patient becomes pregnant while taking study drug)
    - Although pregnancy is not technically an AE, all pregnancies must be followed to conclusion to determine their outcome. This information is important for both drug safety and public health concerns. It is the responsibility of the Investigator or designee to report any pregnancy in a patient that occurs during this study to Panoptes Pharma GesmbH or their representative.

- Accidental exposure (someone other than the study patient was exposed to study drug)
- Overdose (patient received more than the prescribed dose of study drug within a given timeframe)
- Other medication errors that potentially place patients at a greater risk of harm than was previously known or recognized (e.g., study drug was administered by an incorrect route)

8. DRUG SUPPLIES

8.1 PP-001

The active substance being investigated in this study is PP-001. Physicochemical properties are presented in the PP-001 Investigator's Brochure.

The drug product for intraocular administration is supplied by the Sponsor as a 1 mg/ml concentrate solution (PP-001 concentrate for intravitreal injection). Together with the concentrate solution, a sterile sucrose solution for dilution will be provided. A description of the unit formula of the concentrate formulation is provided in the PP-001 Investigator's Brochure.

Preparations with different concentrations of active pharmaceutical ingredient will be administered in order to achieve the desired dose escalation. The highest administered dose of PP -001 in the planned trial will be 2.1 µg and the lowest dose will be 0.3 µg. The corresponding dilution ratios for dilution of the PP-001 concentrate solution (1 mg/mL) with the dilution liquid in the hospital pharmacy are presented in Table 4.

Table 4 Dilution of the Investigational Medicinal Product in the Hospital Pharmacy

Dilution	1 : 47	1 : 82.5	1 : 165	1 : 330
Concentration after dilution, mg/mL	0.021	0.012	0.006	0.003
Volume of PP-001 concentrate for intravitreal injection (1 mg/mL) to be diluted with 33 mL of the dilution liquid, mL	0.7	0.4	0.2	0.1
PP-001 dose (per 0.1 mL injected solution), µg	2.1	1.2	0.6	0.3

A defined volume of the concentrate solution (0.1 – 0.7 mL of PP 001 concentrate for intravitreal injection [1 mg/mL]) will be added directly into the bottle containing exactly 33 mL of the dilution liquid and mixed in order to obtain the dosing solution with the desired PP-001 concentration.

The final PP-001 dosing solutions will always be injected at a volume of 100 µL.

8.1.1 Packaging and Labelling

Study drugs will be packaged and labelled in accordance with the applicable regulatory authority requirements.

8.1.2 Storage of Study Drugs

Access to all study drugs must be restricted to designated study personnel throughout the study.

PP-001 will be stored between 15 and 25°C.

8.1.3 Product Accountability

The Investigator is responsible for study medication accountability, reconciliation and record maintenance. In accordance with all applicable regulatory requirements, the Investigator or designated study site personnel must maintain study drug accountability records throughout the course of the study. This person(s) will document the amount of study drug received from the supplier, the amounts dispensed to patients as well as lot numbers and expiration/retest date of study medications.

At the conclusion of the study, any unused study drug will either be returned to a Sponsor-designated recipient or destroyed at the site after discussion with the Sponsor. If no supplies remain, this will be recorded in the drug accountability section of the final monitoring report.

All unused study drug provided by the Sponsor will be retained for purposes of drug accountability. In addition, empty and partially used vials of PP-001 will be retained by the pharmacy for the purposes of drug accountability. Every effort will be made to retain used containers of PP-001 in the pharmacy for the purposes of drug accountability.

A member of the Sponsor's clinical operations staff (or designee) will check the supplies storage, dispensing procedures and records at regular intervals throughout the study.

9. STATISTICAL ANALYSIS

Statistical analyses of the primary and secondary outcomes will be conducted as outlined below. Descriptive statistics, including the numbers and percentages for categorical variables, and the numbers, means, standard deviations, medians, minimums, and maximums for continuous variables will be provided. Additional statistical analyses, other than those described in this section, may be performed if deemed appropriate. A description of the statistical analysis performed on the study data will be outlined in the Statistical Analysis Plan.

9.1 Treatment Comparison of Interest

The relationship between safety and efficacy results and exposure to PP-001 will be investigated.

9.2 Sample Size Determination

Eighteen patients will be enrolled in the study. No power calculations will be performed and the sample size is based on the requirements of the study design.

9.3 Analysis Populations

9.3.1 Intent-to-Treat Analysis Set

The Intent-to-treat (ITT) Analysis Set will consist of all patients regardless of whether or not the patient received study drug.

9.3.2 Per-protocol Analysis Set

The Per-protocol (PP) Analysis Set will consist of all ITT Analysis Set patients who have no major protocol deviations and who complete the study up to the end of the post-study assessments.

9.3.3 Safety Analysis Set

The Safety Analysis Set will consist of all randomized patients who receive any amount of study drug. All safety analyses will be conducted in this population.

9.3.4 Pharmacokinetic Analysis Set

All patients who receive any amount of study drug will be included in the formal analysis of pharmacokinetic parameters providing they have at least one evaluable pharmacokinetic sample.

9.4 Criteria for Evaluation

9.4.1 Safety Analysis Variables

Safety and tolerability of PP-001 as measured by treatment-emergent AEs (TEAEs) and vital signs.

9.4.2 Pharmacokinetic Analysis Variables

The concentration of PP-001 in plasma at Screening, 4 h ± 1 h after dosing and on Day 2.

9.4.3 Efficacy Analysis Variables

The improvement of inflammation – or any other parameter – as shown by ophthalmic examination.

9.5 Demographic and Baseline Characteristics

Enrolment, protocol deviations and discontinuations from the study drug and the study will be summarized. Demographics (age, race, ethnicity and sex), medical and surgical history and study drug administration will also be summarized by treatment group.

9.6 Safety Analysis

Safety will be evaluated in the Safety Analysis Set by presenting summaries of AEs and vital signs.

Summary tables will be provided for all TEAEs. A treatment-emergent AE is defined as an AE with a start date and time on or after the first dose of study drug. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). The number and percentage of patients with TEAEs will be tabulated by system organ class and MedDRA Preferred Term for each treatment group and by severity and relationship to treatment.

Adverse events leading to premature discontinuation from the study drug and serious TEAEs will be presented either in a table or a listing.

Descriptive statistics of vital signs and the change from baseline for each scheduled evaluation will be summarized at each study visit and the worst overall post-baseline value will be provided. The number and percent of patients with treatment-emergent values with potential clinical significance will be tabulated.

9.7 Pharmacokinetic Analyses

The concentration of PP-001 in plasma will be measured in blood samples taken at Screening, 4 h ± 1 h after dosing and on Day 2.

9.8 Efficacy analysis

All efficacy endpoints will be presented in terms of descriptive statistics.

The relationship between the change from baseline of an efficacy endpoint and exposure to PP-001 will be investigated.

9.9 Handling of Missing Data

Missing values will not be imputed.

9.10 Interim Analysis

The results from each dosing day of the first cohort will be reviewed before progressing with the subsequent dosing day. The next cohort will only commence with dosing after the previous cohort has completed all study sessions up to day 28 and no safety issues have been identified after being reviewed by the SDMB.

After a total of 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 dose with a higher amount of PP-001 will be given to Cohort 4 comprising of four patients. The dose for a potential Cohort 4 will be defined after completion of Cohorts 1 to 3.

If safety issues have been identified in any of Cohorts 2 to 4, then two additional patients will receive the next lower dose.

10. STUDY MONITORING

10.1 Clinical Monitoring

All aspects of the study will be carefully monitored by the Sponsor's authorized individuals, acting as agents of the sponsor with respect to current GCP and Standard Operating Procedures for compliance with applicable government regulations. These individuals will have access to all records necessary to ensure integrity of the data and will periodically review the progress of the study with the Principal Investigator.

Frequent communication between the study site and the Sponsor is essential to ensure that the patient safety is monitored adequately. The Investigator will make safety assessments on an ongoing basis. The Sponsor's medical monitor will review safety information from all study sites as it becomes available throughout the study.

10.2 Safety Data Monitoring Board

Safety will be assessed by monitoring the results of the ophthalmic examinations and AEs throughout the study. Risk assessments will be made by the SDMB after each cohort in written form and throughout the study based on the above. For details please refer to SDMB policy.

11. INDEPENDENT ETHICS COMMITTEE APPROVAL

The Principal Investigator agrees to provide the Independent Ethics Committee (IEC) with all appropriate material, including a copy of the informed consent. The study will not be initiated until the Investigator obtains written approval of the research plan (protocol) and the informed consent document from the appropriate IEC and copies of these documents are received by Panoptes Pharma GesmbH.

It is the Investigator's responsibility to obtain IEC approval for all subsequent major changes to the protocol, in compliance with local law. Appropriate reports on the progress of this study will be made by the Investigator to the IEC and Sponsor in accordance with applicable government regulations and in agreement with policy established by the Sponsor.

12. ETHICAL CONDUCT OF THE STUDY

This clinical study will be conducted in compliance with this Protocol, will be conducted in accordance with the 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), GCP and the current national regulations and guidelines, approved by both the local ethics committee and regulatory authority.

13. INFORMED CONSENT

The International Conference on Harmonization (ICH) has issued guidelines to provide protection for human patients in clinical investigations. The ICH Tripartite Guideline for GCP establishes the general requirements for informed consent.

A properly executed, written informed consent in compliance with the terms of these guidelines shall be obtained from each patient before entering the study, or before performing any unusual or non-routine procedure in relation to the study. The purpose of the study, procedures to be carried out, and potential hazards will be described to each potential patient in non-technical terms. Patients (or their legally authorized representative) will be required to read, voluntarily sign, and date an informed consent form summarizing the discussion at Screening, and will be assured that they may withdraw from the study at any time without jeopardizing their medical care.

Patients will sign and date one copy of the informed consent form, which will be photocopied. The copy will be retained by the patient and the original will be retained on file by the Investigator.

The consent form must be approved by the appropriate IEC and Sponsor before study initiation at a study site. Any subsequent changes to the approved informed consent form must be reviewed and approved by the appropriate IEC and Sponsor before implementation.

14. QUALITY ASSURANCE/QUALITY CONTROL

Standard Operating Procedures belonging to Panoptes Pharma GesmbH or designee(s) will be adhered to for all activities relevant to the quality of the study and are routinely monitored by the Quality Assurance (QA) Division.

Data will undergo quality control checks before clinical database lock. Sponsor-designated, independent monitors will be responsible for monitoring the study and its data within the eCRFs.

A QA audit of this study may be conducted by the Sponsor or Sponsor's designee. The QA auditor will have access to all medical records, the Investigator's study-related files and correspondence and information in the informed consent documentation of this study.

An inspection of this study may be conducted by a regulatory agency. The Investigator agrees to contact the Sponsor as soon as possible, but not later than within 1 week, upon notification of an inspection by a regulatory agency. The Investigator agrees to allow the Inspector direct access to all relevant documents and to allocate his/her time and that of study site personnel to the Inspector to discuss findings in any relevant issues. The Investigator will allow Sponsor personnel to be present as an observer during a regulatory inspection, if requested.

15. DATA HANDLING AND RECORD KEEPING

15.1 Data Handling

Data will be recorded at sites using eCRFs and reviewed by the Sponsor or designee during monitoring visits. The recorded data in the eCRF system will be verified with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail

in the eCRF system. The eCRFs will be considered complete when all missing, incorrect, and/or inconsistent data have been accounted for. Data collected at baseline will only be entered into the eCRF if the patient is eligible for study participation following review of the data by the Investigator or designee.

Adverse events, concomitant medication data and clinical observations will be in the patients' hospital notes, or recorded on source data forms, and will be transferred into the eCRF after assessment by the Investigator or designee.

Data produced by automatic devices with original print-outs (e.g., BP measurements) will be included in the source documentation. Any results outside the normal range should be designated by the Investigator or designee as "clinically significant" or "not clinically significant".

15.2 Patient Confidentiality

The Investigator and his/her staff will be required to manage patient data collected for the study in accordance with applicable laws and regulations on personal data protection.

Data collected during this study may be used to support the development, registration, or marketing of PP-001. Panoptes Pharma GesmbH will control all data collected during the study, and will abide by the EU Directive on Data Privacy concerning the processing and use of patients' personal data. For the purpose of data privacy legislation, Panoptes Pharma GesmbH will be the data controller.

After patients have consented to take part in the study their medical records and the data collected during the study will be reviewed by Panoptes Pharma GesmbH or its representatives. These records and data may, in addition, be reviewed by the following: independent auditors who validate the data on behalf of Panoptes Pharma GesmbH; third parties with whom Panoptes Pharma GesmbH may develop, register, or market PP-001; national or local regulatory authorities and the IECs that gave approval for this study to proceed.

Patients will be known by a unique number; however, their date of birth can also be collected if not in contradiction with any requirements (e.g., from IECs) and used to assist Panoptes Pharma GesmbH to verify the accuracy of the data, for example, that the laboratory results are assigned to the correct patient. The results of this study may be recorded and transferred to and used in other countries throughout the world, which may not afford the same level of protection that applies within the EU. The purpose of any such transfer would be to support regulatory submissions in other countries.

15.3 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

15.4 Data Entry

Data must be recorded using the eCRF system as the study is in progress. All study site personnel must log into the system using their secure user name and password in order to enter,

review, or correct study data. These procedures must comply with EU Directives 2001/20/EC and 2005/28/EC for EU sites. All passwords will be strictly confidential.

15.5 Data Validation

Validation checks programmed within the eCRF system as well as supplemental validation performed via review of the downloaded data will be applied to the data in order to ensure accurate, consistent and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator who signed the protocol.

15.6 Record Keeping

Raw data generated in connection with this study as well as an original copy of the final clinical study report, will be retained in archive until at least 5 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 5 years have elapsed since the formal discontinuation of clinical development of PP-001. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/Institution as to when these documents no longer need to be retained.

As required under European Directive 2005/28/EC, Article 17, all 'essential documents' (as described in the ICH GCP Guidelines) must be retained by Panoptes Pharma GesmbH and the Investigator for at least 5 years after the completion of the clinical study. Therefore, all studies, independent of where they were conducted in the world, must follow this requirement in the event a submission is ever made in the EU. These documents may be retained for a longer period; however, if required by the applicable regulatory requirements or by an agreement with Panoptes Pharma GesmbH. It is the responsibility of Panoptes Pharma GesmbH to inform the Investigator as to when these documents no longer need to be retained. The Investigator must obtain written permission from Panoptes Pharma GesmbH before the destruction of any study document.

These records must be made available at reasonable times for inspection and duplication, if required, by national or foreign Regulatory Authorities in accordance with regulatory requirements.

16. FACILITIES

This study will be performed in up to twelve sites in Europe.

The following analytical laboratory will perform the determination of PP-001 in plasma:
A&M GmbH
Kopernikusstrasse 25
50126 Bergheim
Germany

Managing directors: Dr Axel Römer, Dr Tobias Klaassen
Phone: +49-2271-4787-0 Fax: +49-2271-4787-44

17. TERMINATION OF STUDY

The Sponsor reserves the right to discontinue this study at any time. However the safety of the patients will never be compromised and treated patients will always get at least all schedules follow up visits.

18. FINANCING AND INSURANCE

The costs necessary to perform the study will be agreed with each Investigator and will be documented in a separate financial agreement that will be signed by the Investigator and Panoptes Pharma GesmbH, before the start of the study.

The Investigator will be required to disclose any financial arrangement whereby the value of the compensation for conducting the study could be influenced by the results or outcome of the study. The following information will be collected: any significant payments of other sorts from Panoptes Pharma GesmbH, (e.g., money to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria); any proprietary interest in PP-001; any significant equity interest in Panoptes Pharma GesmbH as defined in 21 CFR 54 2(b).

In consideration of participation in the study, Panoptes Pharma GesmbH will pay the Investigator or nominated payee the sums set out in the payment schedule attached to the Investigator agreement.

19. PUBLICATION POLICY

It is intended that the results of the study may be published as scientific literature. Results may also be used in submissions to Regulatory Authorities. The following conditions are to protect commercial confidential materials (e.g., patents, etc.), not to restrict publication.

All information concerning PP-001 (such as patent applications, formulae, manufacturing processes, basic scientific data, or formulation information supplied to the Investigator by Panoptes Pharma GesmbH and not previously published) is considered confidential by Panoptes Pharma GesmbH and shall remain the sole property of Panoptes Pharma GesmbH. The Investigator agrees not to use it for other purposes without written consent from Panoptes Pharma GesmbH.

It is understood by the Investigator that Panoptes Pharma GesmbH will use the information developed in this clinical study in connection with the development of PP-001 and, therefore, may be disclosed as required to other Panoptes Pharma GesmbH Investigators or any appropriate international Regulatory Authorities. In order to allow for the use of information derived from this clinical study, the Investigator understands that he/she has an obligation to provide Panoptes Pharma GesmbH with complete test results and all data developed during this study.

Before submitting the results of this study for publication or presentation, the Investigator will allow Panoptes Pharma GesmbH at least 30 days in which to review and comment upon the

publication manuscript (or presentation materials). Panoptes Pharma GesmbH agrees that before it publishes any results of this study, it shall provide the Investigators at least 30 days for full review of the publication manuscript. In accordance with generally recognized principles of scientific collaboration, co-authorship with any Panoptes Pharma GesmbH personnel will be discussed and mutually agreed upon before submission of a manuscript to a publisher.

All manuscripts, abstracts or other modes of presentation arising from the results of the study must be reviewed and approved in writing by Panoptes Pharma GesmbH in advance of submission. The review is aimed at protecting Panoptes Pharma GesmbH's proprietary information existing either at the date of the commencement of the study or generated during the study.

The detailed obligations regarding the publication of any data shall be set out in the agreement between each Investigator and Panoptes Pharma GesmbH.

20. LIST OF REFERENCES

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21. APPENDICES

21.1 Appendix 1: Clinical Laboratory Tests

Blood and urine samples for the following will be sent to a local laboratory for testing.

Hematology

- Coagulation panel (including prothrombin time with international normalized ratio and partial thromboplastin time)
- Complete blood count with red blood cell indices and white blood cell differential
- Reticulocyte count
- Platelet count

Chemistry

- Blood urea nitrogen
- Creatinine
- Glucose, fasting
- Sodium
- Potassium
- Chloride
- Calcium
- Magnesium
- Phosphorus
- Aspartate aminotransferase
- Alanine aminotransferase
- Gamma-glutamyl transpeptidase
- Alkaline phosphatase
- Creatinine phosphor-kinase
- Total bilirubin
- Direct bilirubin
- Uric acid
- Albumin
- Total protein

Urinalysis

- Specific gravity
- pH, glucose, protein, blood, ketones, bilirubin, and leukocyte esterase by dipstick
- Microscopic examination (all samples)

21.2 Appendix 2: Values of Potential Clinical Concern

Haematology
Hemoglobin Males: < 12.0 or > 18.0 g/dl Females: < 10.5 or 16.1 g/dl
Hematocrit Males < 36.0 or > 54.0% Females: < 31.0 or > 50.6%
Leukocytes > 1 K/µl below or > 3 K/µl above the limit of the reference range
Platelets < 80 or > 500 K/µl
Chemistry
Total bilirubin ≥ 1.5 times upper limit of the reference range
AST > 2 times upper limit of the reference range
ALT > 2 times upper limit of the reference range
GGT > 2 times upper limit of the reference range
Alk Phosphatase > 1.5 times upper limit of the reference range
Creatinine > 1.8 mg/dl
BUN > 1.5 times upper limit of the reference range
Glucose, fasting < 60 or >126 mg/dl
Uric acid > 11 mg/dl
Sodium > 5 mEq/l above or below the limits of the reference range
Potassium > 0.5 mEq/l above or below the limits of the reference range
Calcium < 7.2 or > 12 mg/dl
Phosphate > 0.8 mg/dl below or 1.0 mg/dl above the limits of the reference range
Albumin > 0.5 g/dl above or below the limits of the reference range
Total protein > 1.0 g/dl above or below the limits of the reference range
Urinalysis
WBC > 15/hpf
RBC > 15/hpf
Vital Signs
Heart Rate Supine: < 35 or > 120 bpm Erect: < 40 or > 140 bpm
Blood Pressure Systolic > 30 mmHg change from baseline in same posture

Diastolic >20 mmHg change from baseline in same posture

21.3 Appendix 3: ECG Values of Potential Clinical Concern

Electrocardiogram
PR interval < 120 ms; ≥ 220 ms
QRS interval ≥ 120 ms
QTc interval(Bazett's)
> 470 ms (adult females ≤ 50 yrs old)
> 480 ms (adult females > 50 yrs old)
> 470 ms (adult males)

Rhythms of Potential Clinical Concern
-Asymptomatic Marked Sinus Bradycardia (rate < 35 bpm)
-Asymptomatic Supraventricular Couplets, Atrial Bigeminy lasting > 30 seconds
-Asymptomatic Ventricular Couplets, Ventricular Bigeminy lasting > 30 seconds
-Asymptomatic Type I Second Degree (Wenckebach) AV Block of > 30 seconds duration
-Asymptomatic Frequent Premature Ventricular Complexes (PVCs) (≥ 144/24 hours)
-Asymptomatic Frequent Premature Atrial Complexes (PACs) (≥ 240/24 hours)

Adverse Experiences
-Symptomatic Marked Sinus Bradycardia (rate < 40 bpm)
-Asymptomatic Sinus Pause > 3 seconds without an escape beat
-Asymptomatic Atrial Flutter or Fibrillation, subcategorized by ventricular response rate: controlled = rate < 120 bpm; rapid = rate ≥ 120 bpm
-Asymptomatic Supraventricular Tachycardia ≥ 3 beats (rate ≥ 120 bpm)
-Asymptomatic Nonsustained Ventricular Rhythms ≥ 3 beats, but duration of < 30 seconds, including idioventricular rhythm (rate < 40 bpm), accelerated idioventricular rhythm (40 ≤ x < 100) and monomorphic/polymorphic ventricular tachycardia ≥ 100 bpm (such as Torsade des pointes)
-Asymptomatic Type II Second Degree (Mobitz) AV Block
-Asymptomatic Complete (third degree) Heart Block

Serious Adverse Experiences
-Sustained Ventricular Arrhythmias (> 30 seconds duration)
-Ventricular Fibrillation

-At the discretion of the investigator, any arrhythmia classified as an adverse experience

21.4 Appendix 4: Investigator Signature Page

INVESTIGATOR SIGNATURE PAGE

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

(Protocol PP-001-1001)

In conducting this clinical study, I agree to be responsible for:

- Ensuring that the clinical investigation is conducted according to the World Medical Association Declaration of Helsinki (revised version of Edinburgh, Scotland, 2000, Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002), the guidelines of International Conference on Harmonization (ICH) Good Clinical Practice (CPMP/ICH/135/95), and other applicable local and national laws and requirements
- Protecting the rights, safety, and welfare of patients under my care
- Maintaining control of the drugs under investigation

I also agree to conduct the study as detailed in the protocol and in accordance with Panoptes Pharma GesmbH guidelines and all applicable government regulations. These guidelines and regulations include, but are not limited to:

- Permission to allow Panoptes Pharma GesmbH and regulatory agencies, to inspect study facilities and pertinent records at reasonable times and in a reasonable manner, which ensures patient confidentiality. If I am notified that this study is to be inspected by a regulatory agency, I will notify Panoptes Pharma GesmbH as soon as possible thereafter (no later than 1 week)
- Submission of the proposed clinical investigation, including the protocol, the informed consent documents, and any other patient materials required for study conduct, to a duly constituted Independent Ethics Committee (IEC)
- Obtaining written informed consent only after ensuring that the patient, or his/her legal representative, is competent to make the decision, understands what is contained in the informed consent document, and is consenting voluntarily. Written informed consent will be obtained prior to administration of study drug or any non-routine study-related procedures; the document contains all the essential elements of consent and has been previously approved by the sponsor and IEC. Reference of written informed consent will be provided in source documentation
- Submission of any protocol amendment to the IEC. If the protocol amendment change(s) increase risk to the study population, full IEC written approval must be obtained prior to implementation. For changes that do not involve increased risk or affect the validity of the investigation or the patient's rights, prior IEC approval may be obtained by expedited review
- Adherence to the study protocol. Documentation and explanation of individual post-enrolment protocol deviations will be recorded in the source documentation at the site and be provided to Panoptes Pharma GesmbH

- Notification to Panoptes Pharma GesmbH of all serious adverse events (SAEs), regardless of relationship to study drug, as specified in the protocol. Notification to the IEC of SAEs as specified in the protocol and per additional guidelines as provided by the IEC
- Notification to IEC of all unanticipated problems within the timeframe provided by the IEC. For the purposes of this study, unanticipated problems are defined as any incident, experience, or patient outcome that meets **all** of the following criteria: (1) unexpected; (2) related or possibly related to participation in the study; (3) and suggests that the research places patients or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known
- Provision of adequate study oversight by personally conducting or supervising the investigation, including, but not limited to: allotting sufficient time to properly conduct and complete the study within the agreed upon time period; having available an adequate number of qualified staff and adequate facilities for the expected duration of the study and to conduct the study properly and safely; and ensuring that all persons assisting with the study are adequately informed about the protocol and the investigational product(s) and are capable of performing their study-related duties and functions. Qualifications of individuals assigned responsibility for the administration of the investigational product will be compliant with state and local law or national regulations, as applicable
- Submission of timely progress reports to the IEC and Panoptes Pharma GesmbH at appropriate intervals not to exceed 1 year and submission of a final report to the IEC within the timeframe set by the IEC, but not later than 3 months after the completion or termination of the clinical investigation
- Maintenance of accurate source records from which case report forms are completed as well as drug accountability records that show the receipt and disposition (on an overall and per patient basis) of all study drug(s) shipped to the Investigator by Panoptes Pharma GesmbH

In addition, I agree to provide all the information requested in the electronic case report form (eCRF) presented to me by Panoptes Pharma GesmbH by carefully following the completion guidelines provided as part of the eCRF.

If I opt to terminate my participation in the study, the foregoing shall equally apply.

_____

Investigator name (print)

_____

Investigator`s signature, Date