Clinical Trial Protocol No. PP-001-1101

A phase I safety and tolerability study of PP-001 eye drops in healthy adult volunteers

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A phase I safety and tolerability study of PP-001 eye drops in healthy adult volunteers (Protocol PP-001-1101)

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PROTOCOL APPROVAL FORM

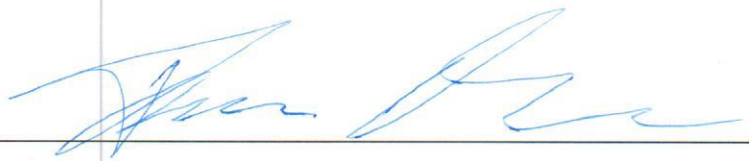
SUBMISSION OF PROTOCOL PP-001-1101

Title: **A phase I safety and tolerability study of PP-001 eye drops in healthy adult volunteers**

(Protocol PP-001-1101)

26. March 2021

NAME	TITLE	DATE
Dr. Franz Obermayr	CEO, Panoptes Pharma	26. March 2021



Signature

INVESTIGATOR SIGNATURE PAGE

A phase I safety and tolerability study of PP-001 eye drops in healthy adult volunteers (Protocol PP-001-1101)

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 revised version of Fortaleza, Brazil 2013), the guidelines of International Conference on Harmonisation (ICH) Good Clinical Practice (CPMP/ICH/135/95), and other applicable local and national laws and requirements
- Protecting the rights, safety, and welfare of subjects 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 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 subject 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)
- Obtaining written informed consent only after ensuring that the subject, 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
- 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 subject 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 subjects 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
- 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 subject 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. Gerhard Garhöfer

Investigator's Name (Please Print)

Investigator's Signature

01/04/2021

Date

SYNOPSIS

Study Title: A phase I safety and tolerability study of PP-001 eye drops in healthy adult volunteers (Protocol PP-001-1101)

Study Objectives:

Primary Objective

The primary objective is to assess the safety and tolerability of 1 day (single dose) and 12 days (48 doses) dosing with ascending doses (0.05% [0.5 mg/mL], 0.15% [1.5 mg/mL] and 0.3% [3.0 mg/mL]) of PP-001 eye drops compared to placebo eye drops in healthy subjects (cohorts 1-3). In addition, safety and tolerability will be tested in a group of 21 patients with ocular surface inflammation (cohort 4).

Secondary Objectives

- To assess the pharmacokinetics of PP-001 eye drops following 1 day (single dose) and 12 days (48 doses) dosing in healthy subjects
- To assess the pharmacodynamics, in relation to the eye, of PP-001 eye drops following 1 day (single dose) and 12 days (48 doses) dosing in healthy subjects and following 12 days (24 doses) dosing in patients with ocular surface inflammation. The following procedures will be used to assess the pharmacodynamics with respect to the eye: Best corrected visual acuity, visual field, intraocular pressure, slit lamp examination, dilated fundoscopy, fundus photography (cohorts 1-3 only), amsler grid.

Study Population:

Inclusion Criteria

Cohorts 1-3:

1. Male or female healthy volunteers 18–64 years of age.
2. Good general state of health (mentally and physically). Laboratory parameters and vital signs of subjects must be within the normal ranges (or judged as not clinically significant by the investigator) and subjects must not have a diagnosis of any eye disease that could affect the pharmacokinetics of PP-001.
3. Willing to provide a signed and dated written informed consent form.
4. Female subjects of childbearing potential must have a negative urine pregnancy test prior to the first administration on Day 0.

5. Male and female subjects 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. Subjects must agree to refrain from becoming pregnant or fathering a child in the 3 months following the last study drug administration. Male subjects must agree with their female partners, prior to screening, to use the above specified methods of contraception while receiving investigational product (IP), and for 3 months after stopping IP.
6. Best-corrected visual acuity of 0.1 log minimal angle of resolution or better in both eyes (approximately 20/25 or better).
7. Intraocular pressure <21 mmHg with differences between eyes of <4 mmHg.

Cohort 4:

1. Male or female subjects 18–64 years of age with ocular surface inflammation in both eyes as defined below.
2. Ocular surface inflammation defined as an Ocular Surface Disease Index (OSDI) of 22 or more AND conjunctival hyperemia of Grade 2 on the Efron Scale or more in both eyes
3. Good general state of health (mentally and physically). Laboratory parameters and vital signs of subjects must be within the normal ranges (or judged as not clinically significant by the investigator) and subjects must not have a diagnosis of any eye disease except ocular surface inflammation.
4. Willing to provide a signed and dated written informed consent form.
5. Female subjects of childbearing potential must have a negative urine pregnancy test prior to the first administration
6. Male and female subjects 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. Subjects must agree to refrain from becoming pregnant or fathering a child in the 3 months following the last study drug administration. Male subjects must agree with their female partners, prior to screening, to use the above specified methods of contraception while receiving IP, and for 3 months after stopping IP.
7. Best-corrected visual acuity of 0.1 log minimal angle of resolution or better in both eyes (approximately 20/25 or better).
8. Intraocular pressure <21 mmHg with differences between eyes of <4 mmHg.

Exclusion Criteria

Cohorts 1-3:

1. Participation in other IP or device clinical trials within 30 days prior to Day 0, or planning to participate in other IP or device clinical trials within 60 days following Day 0. This includes both ocular and non-ocular clinical trials.
2. Female subjects who are pregnant, nursing, or planning a pregnancy, or who are of childbearing potential and not willing to use reliable means of contraception.
3. Subjects with a 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).
4. Subjects who have used regularly any ocular agents within 60 days prior to Day 0.

Cohort 4:

1. Participation in other IP or device clinical trials within 30 days prior to Day 0, or planning to participate in other IP or device clinical trials within 60 days following the first study day. This includes both ocular and non-ocular clinical trials.
2. Female subjects who are pregnant, nursing, or planning a pregnancy, or who are of childbearing potential and not willing to use reliable means of contraception.
3. Subjects with a 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).
4. Subjects who have regularly used any ocular agents within 60 days prior to Day 0 except topical lubricants.

Duration of Study: total duration of study for each subject will be 30 days or more (from screening to last follow-up) in cohorts 1-3 and 22 days or more (from screening to last follow-up) in cohort 4.

Drug Products: PP-001 will be supplied as a ready to use eye drop bottle.

Study Drug Assignment: subjects will be dosed in ascending order with 0.05%, 0.15% and 0.30% PP-001 eye drops depending on the cohort to which they are assigned (cohorts 1-3). Subjects in cohort 4 will be dosed with 0.15% PP-001 eyedrops.

Duration of Treatment: subjects will receive up to four eye drops of PP-001 per day in a randomly assigned eye (cohorts 1-3: 4 drops; cohort 4: 2 drops). Subjects will be treated initially for 1 day (Day 0) and then for 12 days (Days 8–19) in cohorts 1-3 and for 12 consecutive days (Days 0-11) in cohort 4.

Study Drug Administration: PP-001 will be instilled up to four times per day as PP-001 eye drops either by the site staff (MD investigator) or by self-administration.

Blinding: this study is double-blinded within each cohort, the subjects and the investigators do not know if the subject will receive placebo or study drug.

Study Design: this prospective, single-centre, double-blind, placebo-controlled, randomised, parallel-group study will be conducted in accordance with the European Union Clinical Trial Directive 2001/20/EC and 2005/28/EC, the Declaration of Helsinki (revised version of Fortaleza, Brazil 2013), Good Manufacturing Practice, Good Clinical Practice and the current national regulations and guidelines. It will be approved by both the local ethics committee and regulatory authority prior to the first subject being screened.

A total of 24 healthy subjects aged between 18 and 64 years will be included into the first three cohorts of eight subjects each. Each cohort will be performed in two parts. In the first part, subjects will be randomized to receive a single dose of PP-001 or placebo. If safety and tolerability is acceptable, subjects will move on to Part II, where subjects will receive PP-001 or placebo according to the randomization in Part I four times a day for 12 consecutive days. If safety and tolerability is demonstrated in Part II, dose escalation will occur in the next cohort.

- In Cohort 1 six subjects will receive four drops of 0.05% (w/v) PP-001 in only one eye and two subjects will receive placebo in only one eye
- In Cohort 2 six subjects will receive four drops of 0.15% (w/v) PP-001 in only one eye and two subjects will receive placebo in only one eye
- In Cohort 3 six subjects will receive four drops of 0.30% (w/v) PP-001 in only one eye and two subjects will receive placebo in only one eye

Cohorts 1 to 3 will be performed in dose ascending order. On the first two study days in Part I of each cohort, one subject will be dosed per day. On the third study day up to two subjects can be dosed per day. On the following study day(s) up to 4 subjects can be dosed per day. Randomization will be performed in two blocks (3:1, PP-001 vs. placebo) for each cohort. Part II will start at least 7 days after the last subject has been dosed in Part I and the Principal Investigator and the sponsor decide whether or not to continue dosing the cohort in Part II. Within each cohort neither subject nor investigator knows if the subject receives placebo or PP-001. A data safety monitoring board will decide if the safety and tolerability demonstrated in Parts I and II of the previous cohort warrant continuing the study at the next highest dose.

In Cohort 4, twenty-one (21) subjects aged between 18 and 64 years with diagnosed ocular surface inflammation will be included. Subjects will receive half of the highest dose that was considered safe by the DSMB based on the safety data of cohorts 1-3. This cohort will be performed in one part (multiple instillations). Subject will receive two daily instillations for 12 consecutive days (in total 24 administrations). Out of 21 subjects, 14 subjects will receive PP-001 eye drops and 7 subjects will receive placebo. A data safety monitoring board will be installed for safety monitoring of cohort 4.

Statistical Considerations:

Sample Size for cohorts 1-3: Twenty-four (24) healthy female or male subjects will be enrolled in the study. No power calculations have been performed and the sample size is based on the requirements of the study design.

Sample Size for cohort 4: Twenty-one (21) subjects with diagnosed ocular surface inflammation will be treated. No power calculations have been 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 and tolerability.

Analysis Populations

- *Intent-to-treat (ITT) Analysis Set*: all subjects regardless of whether or not the subject received study drug
- *Per-protocol Analysis Set*: all ITT Analysis Set subjects who have no major protocol deviations and who complete the study up to the end of the post-study assessments
- *Safety Analysis Set:* all subjects who receive any amount of study drug. All safety analyses will be conducted in this population
- *Pharmacokinetic Analysis Set:* all subjects 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 physical exam, changes in clinical laboratory parameters, vital signs and adverse events [AEs])

Secondary

- Plasma concentrations of PP-001 and associated derived parameters (cohorts 1-3 only)

Safety analysis

The incidence of treatment-emergent AEs, serious AEs (SAEs), deaths and discontinuations of study drug due to an AE or SAE will be summarised 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 summarised.

Pharmacokinetic analysis

The concentration of PP-001 in plasma will be measured in blood samples taken at Day 0 pre and post dose (0.5 h and 1h ± 5 minutes after dosing) and on Day 8 and 19 at 0.5 h± 5 minutes after last instillation. Samples will be shipped to A&M GmbH, Kopernikusstr. 25, D-50126 Bergheim for analysis. Only subjects of cohorts 1-3 will participate in pharmacokinetic sampling.

Table 1. Schedule of Assessments and Procedures (Cohorts 1-3):

Phase		**Part I**					**Part II**						
	Screening	**Pre dosing**	**Post dosing**	**Telephone call[a]**	**Safety visits**		**Safety visits**						**Follow up**
		Dosing Part I: *Day 0: administration on site					**Dosing* Part II: *Day 8 and 9 (or more): administration on site *Day 10 – Day 19 (or more): self-administration**						
Day	-14 to -2	0	0	1	2	6(+1)	8	9	10(+2)	15(±1)	19	21(±1)	28(±1)
Best corrected visual acuity (ETDRS)	X				X	X	X	X	X	X	X	X	X
Visual field (computerised, 30°)	X					X						X	
Intraocular pressure	X		X		X	X	X[g]	X[g]	X			X	
Slit lamp examination[c]	X	X	X		X	X	X[b]	X[b]	X	X	X	X	
Dilated fundoscopy[d]	X		X[g]		X	X	X[g]	X[g]	X			X	
Blood sampling for PK analysis		X	X[e]				X[h]				X[h]		
Fundus photography	X											X	
Amsler grid	X				X	X	X	X	X	X	X	X	
Urine pregnancy test		X					X						X
Medical and ophthalmic histories	X												
Vital signs[f]	X	X			X	X	X	X	X	X	X	X	
Physical examination[i]	X	X	X										X
Electrocardiogram	X												
Laboratory assessments	X											X	
Concomitant medication		←----------											----------→
Adverse events		←----------											----------→
Evaluation of ocular discomfort		X	X	X	X	X	X	X	X	X	X	X	X
Subject diary of instillation times, AEs and CM		X	X	X	X	X	X	X	X	X	X	X	X

ETDRS: Early Treatment of Diabetic Retinopathy Study; PK: Pharmacokinetic; AE: adverse event; CM: concomitant medications

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 each administration of study drug

c. Conjunctiva (redness standard scales), cornea, anterior chamber, lens

d. Including slit lamp biomicroscopy of the fundus
e. Day 0 blood samples will be taken 30 minutes and 1 hour after instillation
f. Blood pressure and heart rate
g. Examination will be performed after administration of final study drug
h. Day 8 and Day 19 blood samples will be taken 30 minutes after last instillation of the day
i. Height and weight at screening only

* Dosing in part II should be started earliest Day 8 after first administration in part I

Table 2. Schedule of Assessments and Procedures (Cohort 4):

	Screening	**Safety visits**						**Follow up**
		Dosing: ***Day 0 and 1: first administration on site** ***Afterwards: self-administration until day 11**						
Day	-14 to -2	0	1	2(+2)	7(±1)	11	13(±1)	20(±1)
Best corrected visual acuity (ETDRS)	X	X	X	X	X	X	X	X
Visual field (computerised, 30°)	X						X	
Intraocular pressure	X	X[b]	X[b]	X			X	
Tear film osmolarity	X	X[b]	X[b]	X	X	X	X	X
Slit lamp examination[c]	X	X[b]	X[b]	X	X	X	X	X
Tear film break up time	X	X[b]	X[b]	X	X	X	X	X
Corneal staining with fluorescein	X	X[b]	X[b]	X	X	X	X	X
Conjunctival staining using lissamine green	X	X[b]	X[b]	X	X	X	X	X
Dilated fundoscopy[d]	X	X[b]	X[b]	X			X	
Amsler grid	X	X	X	X	X	X	X	
Urine pregnancy test	X	X						X
Medical and ophthalmic histories	X							
Vital signs[e]	X	X	X	X	X	X	X	
Physical examination[f]	X							X
Electrocardiogram	X							
Laboratory assessments	X	X[g]					X	
Concomitant medication		←----------						----------→
Adverse events		←----------						----------→
Evaluation of ocular discomfort[a]		X	X	X	X	X	X	X
Ocular Surface Disease Index	X					X		
Subject diary of instillation times, AEs and CM		X	X	X	X	X	X	X

ETDRS: Early Treatment of Diabetic Retinopathy Study; AE: adverse event; CM: concomitant medications

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. Conjunctiva (Efron scale), cornea, anterior chamber, lens
d. Including slit lamp biomicroscopy of the fundus
e. Blood pressure and heart rate
f. Height and weight at screening only
g. Alcohol and drug screen only

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse event
AKC	Adenoviral keratoconjunctivitis
AUC	Area under the plasma concentration time curve
$AUC_{0-\infty}$	Area under the curve from time 0 to infinity
AUC_{0-24}	Area under the curve from time 0 to 24 h post-dose
BP	Blood pressure
CS	Clinically significant
Cmax	Maximum plasma concentration
DHODH	Dihydroorotate dehydrogenase
DSMB	Data safety monitoring board
EAU	Experimental autoimmune uveitis
ECG	Electrocardiogram
eCRF	Electronic case report form
ETDRS	Early Treatment of Diabetic Retinopathy Study
EU	European Union
FIH	First in human
GCP	Good clinical practice
GMP	Good manufacturing practice
HAV	Human adenovirus
HR	Heart rate
HSA	Human serum albumin
IC_{50}	Half-maximal inhibitory concentration
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
IFN-γ	Interferon gamma
IL-17	Interleukin 17
IP	Investigational product (PP-001)
ITT	Intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
NCS	Not clinically significant
NIU	Non-infectious uveitis
OECD	Organisation for Economic Co-operation and Development
QA	Quality assurance
SAE	Serious adverse event
SRM	Study reference manual
t½	Terminal phase half-life
TEAE	Treatment-emergent adverse event
tmax	Time to maximum concentration

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1. INTRODUCTION

1.1 Adenoviral Keratoconjunctivitis

PP-001 is indicated for the treatment of adenoviral keratoconjunctivitis. This condition is an extremely frequent ophthalmological disease caused by various subtypes of human adenovirus (HAV) which can present with numerous symptoms and signs. Generally, HAV can cause an array of clinical diseases, including conjunctivitis, gastroenteritis, hepatitis, myocarditis and pneumonia. As there is no exact correlation between HAV serotypes and the clinical expressions they produce, adenoviral keratoconjunctivitis is the term used to define ocular surface infections produced by any of the known HAV serotypes. Although exact numbers are difficult to determine, the estimated number of cases of adenoviral conjunctivitis may be as high as 15-20 million per year in the United States (Capriotti et al., 2011) and more than one million cases annually in Japan (Romanowski et al., 2013). The disease is a reportable infection in Germany (Schrauder et al., 2004) and is classified as Category IV infectious disease by Japan´s National Epidemiological Surveillences of Infectious Diseases (NESID) with mandated collection, analysis and publication reports of occurrences (Aoiki et al., 2002). To date, there is no approved antiviral agent for the treatment of these infections available in the European Union (EU) or the United States (US).

Adenoviruses are non-enveloped double-stranded DNA viruses that can infect a variety of human tissues. In adenoviral keratoconjunctivitis, the virus is mainly spread through droplets from tears, however other pathways and fomites are also possible. Through a process known as viral shedding, infectious particles are transferred from extracellular environment of lytic infected cells directly to other host individuals or to objects such as towels, handkerchiefs or facial tissues which in turn can infect other hosts. Actively infected persons readily transmit adenoviruses and viral shedding persists for 12 – 14 days after onset of clinical signs and symptoms (Capriotti et al., 2011).

The condition is usually self-limiting and symptoms tend to last for up to 21 days. However, patients with AKC are highly contagious and HAV can give rise to epidemic outbreaks in the general population and in hospital environments, thus they are constituting a major public health problem. There are numerous reports describing such outbreaks in highly frequented institutions such as schools, swimming pools or hospitals (Warren et al., 1998; Ersoy et al., 2012; Payne et al., 1984, Papapetropoulou et al., 1998). The disease occurs in adults, children and even neonates. Since HAV are very stable against chemical and physical agents as well as variable pH conditions, they can survive for long periods outside the body. It was shown that HAV can maintain infectious concentrations up to 28 days on metal and plastic surfaces, thus remaining an additional potential source for viral transmission (Gordon et al., 1993).

Patients who actively transmit the virus should avoid contact with other potential hosts, therefor absence from work or school for longer periods is usually mandatory. For any new treatment regimen, reduction of viral load and transmission time is desirable to allow patients to return to normal life as soon as possible.

Two major categories of adenovirus ocular infections are distinguished: Epidemic keratoconjunctivitis (EKC) and Pharyngoconjunctival fever (PCF), (Ghebremedhin, 2014). EKC is of low onset and produces large outbreaks in adults and children. Ocular symptoms include irritation, soreness, red eye, photophobia, foreign body sensation and excessive tearing. Other clinical signs may involve swelling and erythema of the lid, conjunctival hyperemia, chemosis,

follicular reaction, papillary hypertrophy or subconjunctival hemorrhage. One of the distinguishing features of EKC is corneal involvement, which is usually mild and transient (Ghebremedhin, 2014). Frequent complications occurring in patients with EKC are the appearance of pseudomembranes and subepithelial infiltrates. If the infiltrates involve the visual axis, photophobia and visual acuity loss can occur and, if untreated, they resolve within a period that can vary between several weeks and even months (Gonzalez-Lopez et al., 2013).

PCF presents with an acute onset accompanied by fever, pharyngitis, rhinitis, cervical adenopathies and bulbar and palpebral conjunctivitis with slight to moderate follicular reaction. The condition lasts approx. 3 – 5 days. PCF causes small outbreaks, mainly among children (Gonzalez-Lopez et al., 2013).

Since no antiviral treatment is currently approved for the treatment of AKC, the assessment of new treatment regimens to treat this condition represents a large unmet medical need in ophthalmology.

1.2 Background on PP-001

The investigational product (IP) used in this study is 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 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 teriflunomide (Aubagio®) are approved for the treatment of rheumatoid arthritis and multiple sclerosis, respectively. PP-001 is structurally and mechanistically distinct from leflunomide. The hepatic metabolism 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 is prepared via a four-step synthesis using commercially available starting materials. An eye drop formulation is being tested in this study.

Further information on PP-001 can be found in the Investigators Brochure [Investigators Brochure, current version].

1.3 Non-Clinical Development

Mechanism of Action and Non-Clinical Pharmacology

Adenoviral keratoconjunctivitis (AKC) is an extremely frequent ophthalmological disease caused by various serological subtypes of human adenovirus (HAV). The condition presents with various signs and symptoms following ocular surface infections by any of the known HAV serotypes. HAV infections are highly contagious and often cause epidemic outbreaks. Treatment of HAV infections with PP-001 is based on preventing viral replication by the inhibition of DHODH.

PP-001 is a third generation small molecule inhibitor of DHODH, with a half-maximal inhibitory concentration (IC_{50}) of below 4 nM (1.9 ng/ml). DHODH is a key enzyme in the *de novo* pyrimide

synthesis pathway and catalyzes the conversion of dihydroorotate (DHO) to orotate. The pathway channels into the production of uridine monophosphate (UMP), which is the precursor for all pyrimidine nucleotides needed for RNA and DNA synthesis. Viral replication and viral cell metabolism depend on a large nucleotide pool, thus it is postulated that the antiviral efficacy of PP-001 is due to pyrimidine depletion caused by DHODH inhibition.

Broad antiviral activity of PP-001 was confirmed in several *in vitro* as well as *in vivo* experiments. PP-001 showed strong DHODH dependent *in vitro* activity against human and animal cytomegaloviruses (CMV) and clinically relevant types of adenoviruses. When administered systemically, PP-001 showed efficacy in a mouse model against CMV infections (Marschall et al., 2013). In a rabbit model for adenoviral keratoconjunctivitis, PP-001 eye drops showed significant reduction of ocular virus load compared to vehicle control.

No safety pharmacology studies have been conducted so far because of the ocular route of PP-001 and consequently the very low systemic exposure following topical use. However, the potential of PP-001 to affect selected safety pharmacology parameters was evaluated as part of a repeated dose toxicity study. In this 14-day intravenous (i.v.) repeated dose toxicity study in rats, PP-001 did not show evidence for adverse effects on safety pharmacology parameter at the highest dose tested (1.0 mg/kg body weight). In addition, inhibition of the hERG channel by PP-001 was not indicated when tested *in vitro* at concentrations well above the intended human exposure. No further stand-alone *in vivo* safety pharmacology studies were planned.

Pharmacokinetics and Product Metabolism

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

PP-001 exhibited strong *in vitro* plasma protein binding (>99.9% binding) and high metabolic stability after incubation with human liver microsomes. Inhibition potential towards human Cytochrome P450 (CYP450) enzymes was detected, but considered insignificant due to a very low systemic PP-001 exposure after topical ocular administration.

Single and multiple administrations of different PP-001 eyedrop formulations (clinical and development formulation) in rabbits resulted in maximum systemic exposure in the low ng/ml range. Maximum PP-001 concentrations in plasma ranged between 9 ng/ml after a single dose of 105 µg PP-001 (clinical formulation) and 23 ng/ml after multiple doses of PP-001 (development formulation; one eye per animal treated 4 times daily over 14 days; 420 µg PP-001 total daily dose).

Ocular tissue concentrations following single and multiple instillations of PP-001 eyedrop formulations were highest in conjunctiva followed by cornea. After a single dose (105 and 91 µg PP-001 per drop for clinical and development formulation, respectively), maximum tissue concentrations ranged between 1.3 ± 0.1 µg/g (clinical formulation) and 12.4 ± 4.9 µg/g (development formulation) in conjunctiva. In cornea, maximum tissue concentration ranged between 0.4 ± 0.04 µg/g (clinical formulation) and 9.4 ± 2.0 µg/g (development formulation).

Multiple topical instillations (4 drops daily over 4 days, 365 µg PP-001 total daily dose per eye, development formulation) resulted in maximum tissue concentrations of 9.2 ± 3.2 µg/g in conjunctiva and 9.3 ± 3.0 µg/g in cornea. No tissue accumulation following multiple dosing over four days compared to a single dose was detected in conjunctiva whereas a slight accumulation

was determined in the corneal tissue (1.9 fold). Half-life of PP-001 after multiple dosing over four days in rabbits was 2.7 hours in conjunctiva, 9 hours in cornea and 1.4 hours in peripheral blood.

PP-001 does not elicit ocular melanin binding properties as shown in an *in vivo* ocular distribution study comparing PP-001 tissue content in pigmented and non-pigmented rats.

Non-Clinical Safety and Toxicology

Non-clinical safety and toxicology studies included single (topical ocular, IVT) and repeated dose (topical ocular, i.v.) toxicity testing in rabbits and rats, *in vitro* genotoxicity testing in bacterial and mammalian cells and *in vitro* phototoxicity testing in BALB/c 3T3 cells. All pivotal non-clinical studies were conducted in a country that is a member of the OECD Mutual Acceptance of Data program in accordance with the OECD Test Guidelines and Principles of Good Laboratory Practice (GLP) and respective ICH and CHMP 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 topical doses in humans and thus an adequate safety margin with respect to systemic toxicity is provided.

In a 14-day repeated dose ocular tolerance study conducted in NZW rabbits, PP-001 was instilled 4 times daily over 14 days (35 µl/application) at concentrations of 0.5, 1.5 and 3.0 mg/ml. Topical instillations of PP-001 were shown to be safe with a no observed adverse effect level (NOAEL) with regard to ocular toxicity at the highest dose level of 3.0 mg/ml. No test item related ocular adverse effects or any other findings in body weight change or food and water consumption were observed in any dose group during the course of the study.

PP-001 did not show genotoxic potential in *S. typhimurium* tester strains and a mouse lymphoma assay. Phototoxicity of PP-001 was not indicated in an *in vitro* 3T3 NRU assay.

1.4 Summary of Clinical Data

A first-in-human clinical study to evaluate the safety of intravitreally applied PP-001 in patients with chronic, non-infectious uveitis has been completed (EudraCT number 2016-000412-15; Protocol number PP-001-1001). In this study, PP-001 was be applied as single, intravitreal injection to 12 patients. The study´s primary objective was to assess the safety and tolerability of ascending doses of PP-001 in patients. The secondary objectives were to assess improvement of intraocular inflammation and to evaluate the pharmacokinetics of PP-001 in patients. In this study, no serious adverse events were reported and intravitreal PP-001 was well tolerated in all dose groups. Assessment of the evaluated efficacy parameter showed a clear dose-response dependent treatment effect in improvement of visual acuity. PP-001 was not detected in any plasma sample of any patient.

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary objective is to assess the safety and tolerability of 1 day (single dose) and 12 days (48 doses) dosing with ascending doses (0.05% [0.5 mg/mL], 0.15% [1.5 mg/mL] and 0.3% [3.0 mg/mL]) of PP-001 eye drops compared to placebo eye drops in healthy subjects. In addition, safety and tolerability of half of the maximum tolerated dose will be tested in a group of 21 patients with ocular surface inflammation.

2.2 Secondary Objectives

- To assess the pharmacokinetics of PP-001 eye drops following 1 day (single dose) and 12 days (48 doses) dosing in healthy subjects.
- To assess the pharmacodynamics, in relation to the eye, of PP-001 eye drops following 1 day (single dose) and 12 days (48 doses) dosing in healthy subjects and following 12 days (24 doses) dosing in patients with ocular surface inflammation.

2.3 Primary Endpoint

The primary endpoint will be safety and tolerability as assessed through:

- Adverse events
- Serious AEs (SAEs)
- Laboratory safety tests
- Concomitant medication
- Vital signs
- Physical examination

2.4 Secondary Endpoints

- The concentration of PP-001 in plasma at predose, postdose (30 min and 1h ± 5 minutes after dosing), day 8 and day 19 (30 min ± 5 minutes after last dosing of the day) will be determined.
- Pharmacodynamic parameters relating to the eye as assessed through:
  - Best corrected visual acuity
  - Visual field
  - Intraocular pressure
  - Slit lamp examination
  - ad slit lamp examination: Conjunctival hyperemia according to the Efron scale (cohort 4 only)

- Dilated fundoscopy
- Fundus photography (cohorts 1-3 only)
- Amsler grid
- OSDI score (cohort 4 only)
- Tear film osmolarity (cohort 4 only)
- Tear film break up time (cohort 4 only)
- Corneal fluorescein staining (cohort 4 only)
- Conjunctival staining using lissamine green (cohort 4 only)

3. STUDY DESIGN

This prospective, single centre, double-blind, placebo-controlled, randomised, parallel-group study will be conducted in accordance with the European Union (EU) Clinical Trial Directive 2001/20/EC and 2005/28/EC, the Declaration of Helsinki (revised version of Fortaleza, Brazil 2013), Good Manufacturing Practice (GMP), Good Clinical Practice (GCP) and the current national regulations and guidelines. It will be approved by both the local ethics committee and regulatory authority prior to the first subject being screened.

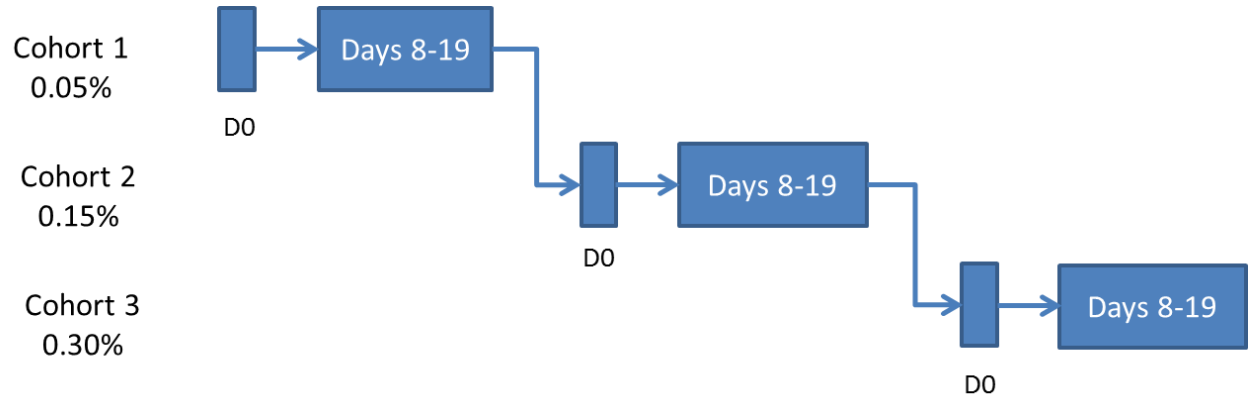
A total of 24 healthy subjects aged between 18 and 64 years will be included into three cohorts of eight subjects each. Each cohort will be performed in two parts. In the first part, subjects will be randomized to receive either a single dose of PP-001 or placebo. If safety and tolerability is acceptable, subjects will move on to Part II, where subjects will receive PP-001 or placebo according to the randomization in Part I four times a day for 12 consecutive days. If safety and tolerability is demonstrated in Part II, dose escalation will occur in the next cohort.

- In Cohort 1 six subjects will receive four drops of 0.05% (w/v) PP-001 in only one eye and two subjects will receive placebo in only one eye
- In Cohort 2 six subjects will receive four drops of 0.15% (w/v) PP-001 in only one eye and two subjects will receive placebo in only one eye
- In Cohort 3 six subjects will receive four drops of 0.30% (w/v) PP-001 in only one eye and two subjects will receive placebo in only one eye

Cohorts 1 to 3 will be performed in dose ascending order. On the first two study days in Part I of each cohort, one subject will be dosed per day. On the third study day up to two subjects can be dosed per day. On the following study day(s) up to 4 subjects can be dosed per day. Randomization will be performed in two blocks (3:1, PP-001 vs. placebo) for each cohort. Part II will start at least 7 days after the last subject has been dosed in Part I and the Principal Investigator and the sponsor decide whether or not to continue dosing the cohort in Part II. A data safety monitoring board (DSMB) will decide if the safety and tolerability demonstrated in Parts I and II of the previous cohort warrant continuing the study at the next highest dose.

The study schematic is presented in Figure 1.

Figure 1: Study Schematic



The actual procedures that should be performed at each time point in cohorts 1-3 are listed in the Time and Events table (Table 1).

The total duration of study for each subject will be 30 days or more (up to 42 days; from screening to last follow-up).

After completion of cohort 1-3 to assess safety and tolerability of PP-001 in different concentrations in healthy subjects, safety and tolerability will be tested in a separate group (cohort 4), namely in patients with ocular surface inflammation, which is the intended target group for PP-001 in the future. In particular, in cohort 4, twenty-one (21) subjects with diagnosed ocular surface inflammation will be included. Subjects will receive half the highest dose that was considered safe by the DSMB based on the safety data of cohort 1-3. This cohort will be performed in one part (multiple instillations). Subjects will receive two daily instillations for 12 consecutive days (in total 24 administrations). Out of 21 subjects, 14 will receive PP-001 eye drops and 7 will receive placebo.

The actual procedures that should be performed at each time point in cohort 4 are listed in the Time and Events table (Table 2).

The total duration of study for each subject in cohort 4 will be 22 days or more (up to 35 days) from screening to last follow-up).

3.1 Study Rationale

PP-001 is being developed for the treatment of non-infectious posterior uveitis.

In a completed study, PP-001 was administered, via intravitreal injection, to subjects with chronic intraocular inflammation, who have either failed to improve on maximal medical treatment or who are unable to tolerate medical treatment because of adverse ocular or systemic effects. In this study, intravitreal PP-001 was well tolerated and no serious AEs were reported.

Although intravitreal injections are used in other treatments for uveitis, such as Ozurdex® and Retisert®, these are unpleasant for the patient and run a small risk of either causing eye infections or an autoinflammatory reaction occurring due to small crystals in the preparation. It is therefore preferable to develop a liquid formulation which can be administered as eye drops. This form of administration should reduce associated side effects and improve patient compliance.

The present study is consequently designed to investigate the safety, tolerability and pharmacokinetics of PP-001, administered as an eye drop formulation following a single dose and following dosing over 12 days (48 doses) in healthy subjects. In addition, safety and tolerability will also be assessed in patients with ocular surface inflammation, using half the maximum of the highest dose tolerated by healthy subjects. The results of this study will be compared with the results seen in PP-001-1001 (intravitreal injection) and used to identify which formulation should be taken forward for development.

As the route of administration is less invasive than the previous study it is felt ethically acceptable to include healthy subjects.

3.1.1 Dose Rationale

For evaluation of a safe human starting dose a calculation based on a mg/kg basis is not considered appropriate for locally applied drugs. However, in the EU there is no applicable guidance available in this regard and thus, reference is made to *FDA's Note for Guidance Estimating the Maximum Safe Starting Dose in Initial Clinical Trials.* For topical ocular products, the concentration and total dose applied is considered most relevant. Since the company does not intend to include patients into the first in human (FIH) study, the starting dose for the upcoming clinical study will not consider data on the minimum efficacious dose of PP-001 following topical application.

For the planned FIH trial a total of three PP-001 formulations with increasing concentration shall be investigated for safety and tolerability using a staged design as outlined below (Table 3):

Table 3: Staged design for clinical trial PP-001-1101 (Cohorts 1-3)

Cohort	Part I*	Part II*
0.5 mg/ml	single dose on single day	4 daily doses over 12 days
1.5 mg/ml	single dose on single day	4 daily doses over 12 days
3.0 mg/ml	single dose on single day	4 daily doses over 12 days

*Each cohort will be performed in 2 parts (part I and part II). In part I, subjects will receive PP-001 a single time on only a single day. If safety and tolerability is acceptable, volunteers will move on to part II, where subjects will receive PP-001 4 times a day for 12 consecutive days. If safety and tolerability is shown in part I and II, the next cohort with the higher dose will be started. Part II will start at least 7 days after the last subject has been dosed in part I and the Principal Investigator and the sponsor decide to continue with the cohort in part II. A data safety monitoring board will decide if the safety and tolerability of the previous cohort part I and II warrants to continue the study with the next higher dose.

For PP-001, the clinical starting dose was evaluated based on the results of the GLP local tolerance study in NZW rabbits (Study No. 16P006). NZW rabbits are known as sensitive and appropriate species for ocular tolerance testing with an extensive use in the past. Thus, it is considered that this species provides adequate information on the safety profile of topical / ocular applied PP-001.

Safety and local tolerability of PP-001 was shown in a GLP 14-day ocular tolerance study (Study No. 16P006) in NZW rabbits (n= 5 males and 5 females per group). A different vehicle formulation compared to the clinical formulation was used in this study. When given 4 times daily PP-001 was

well tolerated up to the highest tested concentration of 3.0 mg/ml, corresponding to a total daily dose of 0.42 mg PP-001 per ocular surface. The ocular surface of rabbits (2.0 – 2.9 kg; ~14.9 cm^2) is slightly smaller compared to the human ocular surface (~18.7 cm^2), therefore exposure of PP-001 (total dose) to the ocular surface of rabbits is 1.2 fold higher compared to humans (Watsky et al., 1988). Consequently, a conversion factor of 1.2 is applied for safety margin calculations.

The concentration of 3.0 mg/ml, which was set as NOAEL with respect to ocular toxicity in this study, is 6-fold above the intended starting concentration of PP-001 in the FIH study (see Table 4). The total daily dose, applied by a single or four consecutive applications with an assumed average drop volume of 40 µl, would show a 26-fold or 7-fold safety margin for part I or part II, respectively.

Even at the highest planned concentration of 3.0 mg/ml, safety margins with respect to local concentration of PP-001 or total dose applied to the human eye is considered being covered by the non-clinical study in rabbits (see Table 4).

Table 4: Calculated Safety Margins to Nonclinical Studies

FIH Cohort	FIH Daily Dose (Part I)*	FIH Daily Dose (Part II)**	NOAEL in NZW Rabbits	FIH Safety Margin		
				Concen -tration	Daily Dose (Part I)***	Daily Dose (Part II)***
0.5 mg/ml	0.02 mg	0.08 mg	>3.0 mg /ml	>0.42 mg	6	26.3	6.6
1.5 mg/ml	0.06 mg	0.24 mg			2	8.8	2.2
3.0 mg/ml	0.12 mg	0.48 mg			1	4.4	1.1

* Calculated based on an application volume of 1 drop /day/eye; an average drop volume of 40 µl is assumed
** Calculated based on an application volume of 4 drops/day/eye; an average drop volume of 40 µl is assumed
*** a conversion factor of 1.2 based on ocular surface area rabbit vs. human is applied

In rabbits, single and repeated instillations of PP-001 (4 times daily over 14 days, up to 3.0 mg/ml) resulted in very low systemic exposure, with maximal plasma levels in the low ng/ml range. The risk for systemic toxicity was evaluated in a GLP study in rats and rabbits. In rats, PP-001 was given *via* the i.v. route at a dose of 1 mg/kg. No signs of toxicity were observed in this study. The obtained maximum plasma levels after 1.0 mg/kg i.v. administration in rats (C_{max} = 11.8 µg/ml) were approx. 500-fold higher than after four daily topical administrations over 14 days in rabbits at a dose of 3.0 mg/ml or 105 µg/drop (C_{max} = 23.1 ng/ml). In rabbits, PP-001 was administered intravitreally in both eyes (30 µg/eye), resulting in an approx. 2-fold higher systemic exposure (C_{max} = 43.5 ng/ml) compared to multiple topical administration (3 mg/ml over 14 days; C_{max} = 23.1 ng/ml) with no observed associated signs of toxicity. Accordingly, no risk for systemic toxicity is expected for all cohorts planned in the FIH study.

Plasma levels following an ocular (topical) dose of 0.48 mg/eye in humans 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 at the eye, the starting dose of the first cohort which will receive a single drop of 0.5 mg/ml PP-001 provides a safety margin of 6 compared to the highest tested safe concentration in rabbits. In conclusion, the proposed starting dose of 0.5 mg/ml or 0.02 mg per eye

provides an adequate safety margin for clinical study PP-001-1101 with respect to local and systemic toxicity.

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, designed to inhibit an enzyme called DHODH, a known drug target for systemic treatment of rheumatoid arthritis and multiple sclerosis. PP-001 is a novel inhibitor of DHODH and has the potential to deliver a new treatment for patients with AKC. Currently, patients suffering from AKC are not treated with any drug-based therapy.

In the present study the safety and tolerability of multiple doses of PP-001, administered via eye drops as a single dose and over 12 days (48 doses), will be evaluated. Based on the pharmacokinetic results from the previous study (PP-001-1001) the ocular half-life is expected to be less than 9 h and the systemic exposure is expected to be below the biological activity and close to or below the limit of detection (10 ng/mL). Therefore, this study poses limited risk to the healthy subjects enrolled.

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

The inclusion and exclusion criteria prevent individuals with eye disorders, which may be adversely affected by exposure to the IP, from entering the study.

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 side effects seen with other DHODH inhibitors are not expected to occur.

In conclusion, based on the currently available safety data, and at doses in the estimated therapeutic range of up to 3.0 mg/mL and four daily drops/eye, PP-001 has an acceptable benefit/risk profile in this study population. Study PP-001-1101 will provide valuable data on the safety, tolerance and pharmacokinetic profile of PP-001 following a single dose and over 12 days (48 doses), via eye drops in healthy subjects, which will help to define the dose and formulation for future studies.

4. STUDY POPULATION

4.1 Inclusion Criteria

Cohorts 1-3:

All subjects must meet all of the following criteria to be included in the study:

1. Male or female healthy volunteers 18–64 years of age.

2. Good general state of health (mentally and physically). Laboratory parameters and vital signs of subjects must be within the normal ranges (or judged as not clinically significant by the investigator) and subjects must not have a diagnosis of any eye or systemic disease that could affect the pharmacokinetics of PP-001.

3. Willing to provide a signed and dated written informed consent form.

4. Female subjects of childbearing potential must have a negative urine pregnancy test prior to the first administration on Day 0.

5. Male and female subjects 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. Subjects must agree to refrain from becoming pregnant or fathering a child in the 3 months following the last study drug administration. Male subjects must agree with their female partners, prior to screening, to use the above specified methods of contraception while receiving IP, and for 3 months after stopping IP.

6. Best-corrected visual acuity of 0.1 log minimal angle of resolution or better in both eyes (approximately 20/25 or better).
7. Intraocular pressure <21 mmHg with differences between eyes of <4 mmHg.

Cohort 4:

All subjects must meet all of the following criteria to be included in the study:

1. Male or female subjects 18–64 years of age with ocular surface inflammation in both eyes as defined below.
2. Ocular surface inflammation defined as an Ocular Surface Disease Index (OSDI) of 22 or more AND conjunctival hyperemia of Grade 2 on the Efron Scale or more in both eyes

3. Good general state of health (mentally and physically). Laboratory parameters and vital signs of subjects must be within the normal ranges (or judged as not clinically significant by the investigator) and subjects must not have a diagnosis of any eye disease except ocular surface inflammation.

4. Willing to provide a signed and dated written informed consent form.

5. Female subjects of childbearing potential must have a negative urine pregnancy test prior to the first administration

6. Male and female subjects 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. Subjects must agree to refrain from becoming pregnant or fathering a child in the 3 months following the last study drug administration. Male subjects must agree with their female partners, prior to screening, to use the above specified methods of contraception while receiving IP, and for 3 months after stopping IP.
7. Best-corrected visual acuity of 0.1 log minimal angle of resolution or better in both eyes (approximately 20/25 or better).
8. Intraocular pressure <21 mmHg with differences between eyes of <4 mmHg.

4.2 Exclusion Criteria

Cohorts 1-3:

Subjects must be excluded if any of the following criteria are met:

1. Participation in other IP or device clinical trials within 30 days prior to Day 0, or planning to participate in other IP or device clinical trials within 60 days following the first study day. This includes both ocular and non-ocular clinical trials.
2. Female subjects who are pregnant, nursing, or planning a pregnancy, or who are of childbearing potential and not willing to use reliable means of contraception.
3. Subjects with a 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).
4. Subjects who have regularly used any ocular agents within 60 days prior to Day 0.

Cohort 4:

Subjects must be excluded if any of the following criteria are met:

5. Participation in other IP or device clinical trials within 30 days prior to Day 0, or planning to participate in other IP or device clinical trials within 60 days following the first study day. This includes both ocular and non-ocular clinical trials.
6. Female subjects who are pregnant, nursing, or planning a pregnancy, or who are of childbearing potential and not willing to use reliable means of contraception.
7. Subjects with a 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).
8. Subjects who have regularly used any ocular agents within 60 days prior to Day 0 except topical lubricants.

5. STUDY DRUG ADMINISTRATION

See Section 8 for a complete description of study drugs. The study drug will be supplied ready to use.

This is a randomised, placebo-controlled study and double blinded within each cohort

Each subject who completes the study screening assessments, meets all eligibility criteria, and is accepted for the study will be assigned a unique identification number and will receive the corresponding study medication (PP-001 or placebo) according to a randomization schedule

Medication will be provided in pre-labelled, blinded, treatment bottles.

The site will be provided with code-break envelopes by which they can break the blind if required. The Investigator should contact the Sponsor prior to breaking the blind unless the subject's safety may be put at risk by doing so.

5.1 Study Drug Treatment

5.1.1 Duration of Treatment

Subjects will receive up to four eye drops of PP-001 per day in a randomly assigned eye. Subjects will be treated initially for 1 day (Day 0) and then for 12 days (4 times daily, Days 8–19) in cohorts 1-3 and for 12 consecutive days (2 times daily, Days 0-11) in cohort 4.

5.1.2 Post-Baseline Treatment Modifications

Cohorts 1 to 3 will be performed in dose ascending order. On the first two study days in Part I of each cohort, one subject will be dosed per day. On the third study day up to two subjects can be dosed per day. On the following study day(s) up to 4 subjects can be dosed per day. Randomization will be performed in two blocks (3:1, PP-001 vs. placebo) for each cohort. Part II will start at least 7 days after the last subject has been dosed in Part I and the Principal Investigator and the sponsor decide whether or not to continue dosing the cohort in Part II. The DSMB will decide if the safety and tolerability demonstrated in Parts I and II of the previous cohort warrant continuing the study at the next highest dose.

Subjects in cohort 4 will instill the eye drops only twice daily.

5.2 Timing of Dosing and Dose Administration

Cohorts 1-3:

Subjects will receive IP on Day 0 (single dose) and then Days 8–19 (48 doses).

On Day 0, the IP dose will be administered in house by site staff. Staff will administer a single drop of IP into one eye.

On Day 8 and 9, the IP doses will be administered in house by site staff. Staff will administer a single drop of IP into one eye four times throughout the dosing day separated by at least 4 hours.

On Days 10–19, the IP will be self-administered. Subjects will administer a single drop of IP into one eye four times throughout each dosing day separated by at least 4 hours.

Cohort 4:

Subjects will receive IP on Days 0-11 (24 doses).

On Day 0 and 1, the first instillation will be performed in house by site staff. Staff will administer a single drop of IP into one eye. At all following time points, the IP will be self-administered. Subjects will administer a single drop of IP into one eye two times throughout each dosing day separated by at least 8 hours.

Since only one randomly assigned eye will be treated, subjects will be handed out a bottle of topical lubricants (Genteal HA, Laboratoires Thea, France) as standard of care treatment for the control eye as needed. Subjects will be instructed to document instillation dates and times for Genteal HA eye drops in the diary.

5.3 Preparation of Treatment

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

5.4 Blinding

This is a double-blind study within each cohort. Subjects will receive either PP-001 or placebo. Randomization will be done in two blocks of 4 subjects per block (3:1, PP-001 vs. placebo) for each of the three cohorts (cohorts 1-3). For cohort 4, randomization will be performed in a 2:1 ratio (14 subjects will receive the PP-001 and 7 will receive placebo). Subjects within one cohort will not be aware whether they are receiving PP-001 or placebo. The investigators will not know whether a subject receives PP-001 or placebo within a cohort. The IP will be provided in pre-packaged eye drop bottles which will be labelled in a double-blind fashion.

5.5 Unblinding of Therapy Assignments

Breaking of the blind (active or placebo), by opening an emergency envelope, is expressly forbidden except in the event of a medical emergency where the identity of the drug must be known in order to properly treat the subject. In the event of such an emergency, it is requested that the investigator make every effort to contact the Sponsor medical representative, or Sponsor project manager prior to breaking the code. In all cases, the clinical study monitor must immediately be informed of occasions where a code has been broken. Contact details of the clinical study monitor will be provided by the Sponsor prior to the start of the study and will be readily available to all relevant site personnel at all times.

The date and time of unblinding, the name of the study personnel responsible, and the reason for the unblinding must be documented in the CRF and on the document provided in the individual code-break envelope. If the code for an individual subject is broken at the site, the monitor must be notified as soon as possible. In each case where the code is broken, that subject must be excluded from the study.

After completion of the study and after the final report has been signed, all the code-break envelopes, whether opened or not, will be returned, by the clinic pharmacy staff, to the sponsor and filed in the trial master file.

5.6 Adherence

Cohorts 1-3:

During dosing on Days 0, 8 and 9 of the study, hospital staff or study personnel will administer all doses of study drug. The date and time of each dose will be recorded in the electronic case report form (eCRF).

During dosing on Days 10–19 of the study, the subject will self-administer all doses of study drug. The date and time of each dose will be recorded in a diary card and will be transcribed by site staff into the eCRF. Subjects will be counted as compliant with the study if they receive at least 90% of the scheduled doses during Days 9–19.

Cohort 4:

First dosing on Day 0 and 1 will be performed by hospital staff or study personnel. The date and time of each dose will be recorded in the electronic case report form (eCRF).

All other doses will be self-administered by the subjects. The date and time of each dose will be recorded in a diary card and will be transcribed by site staff into the eCRF. Subjects will be counted as compliant with the study if they receive at least 90% of the scheduled doses during Days 0–11.

5.7 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 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 PROCEDURES

A schedule of study procedures is presented in Table 1 and Table 2. Subjects 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.

The day on which PP-001 is first 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 subject's eCRF.

For subjects 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 Safety Assessments

6.1.1 Medical and Ophthalmic History

A medical and ophthalmic history will be taken at the times outlined in the Time and Events table (Table 1 and Table 2). 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 by the Investigator to the conduct of the study. The medical history should include drug allergy history and past and present smoking status.

6.1.2 Vital Signs

Vital signs (heart rate [HR] and blood pressure [BP]) will be recorded at the times outlined in the Time and Events table (Table 1 and Table 2). Blood pressure and HR will be assessed after the subject has been in a sitting position for 10 minutes. Study personnel will record vital signs measurements in the eCRF.

Vital signs measurements are to be repeated if clinically significant changes or machine errors occur. Out of range measurements (according to site normal ranges) will be repeated at the Investigator's discretion. Sitting BP and HR will be measured more frequently if warranted by the clinical condition of the subject.

6.1.3 Physical Examination

A complete physical examination will be performed by the Investigator at the times outlined in the Time and Events table (Table 1 and Table 2). This should include a review of the head, ears, nose, throat, skin, thyroid, neurological system, lungs, cardiovascular system, lymph nodes and extremities.

Body weight and height will be measured at Screening only.

6.1.4 Electrocardiogram

Triplicate 12-lead electrocardiograms (ECGs) will be performed within a 5-minute interval at the time points outlined in Table 1 and Table 2.

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. Subject with findings of clinical significance will not be eligible to participate in the clinical study.

6.1.5 Clinical Laboratory Tests

Safety laboratory tests will be performed at the times outlined in the Time and Events table (Table 1 and Table 2) and sent to a local laboratory or evaluated at the clinical site, if appropriate. 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 analysed is presented in Section 21.1.

Any clinical significant 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 occurring during the study period should be repeated as necessary and followed until resolution.

6.1.6 Urine Pregnancy Test

Urine samples should be collected from women of child-bearing potential at the times outlined in the Time and Events table (Table 1 and Table 2). Urine pregnancy tests should be performed according to the site's standard procedures.

Any woman with a positive pregnancy test should be withdrawn from the study and the Sponsor notified as outlined in Section 7.4.

6.1.7 Evaluation of Ocular Discomfort

An evaluation of ocular discomfort will be performed by the Investigator at the times outlined in the Time and Events table (Table 1 and Table 2). A global ocular discomfort score will be determined using a 100 mm VAS on which 0 means no symptoms and 100 means the worst possible discomfort. The following symptoms will be assessed:

Burning
Stinging
Itching
Foreign body sensation
Blurred vision

6.2 Sample Collection for Pharmacokinetic Analysis

6.2.1 Plasma Sample Collection

Blood samples for pharmacokinetic analysis of PP-001 in plasma following dosing will be collected at the times outlined in the Time and Events table (Table 1).

Blood samples will be collected into tubes containing tri-potassium ethylenediaminetetraacetic acid, immediately chilled on crushed ice, and then centrifuged at approximately 2000 g for approximately 10 minutes at +4°C to separate plasma. Following centrifugation, plasma specimens will be transferred as 2 equal aliquots (aliquot A and B) in microtubes. Plasma tubes have to be

labelled at least with the following information: PP-001-1101, subject number, sample ID (day 0, predose; day 0, 30 min; day 0, 60 min; day 8; day 19), aliquot ID (A or B). Promptly following centrifugation, plasma samples will be immediately frozen and stored at -20ºC or cooler until transported. The total time from blood withdrawal to storage of plasma at -20ºC should not exceed 60 minutes. The primary samples (aliquot A) will be transferred on dry ice to A&M GmbH for analysis.

6.2.2 Assay Methodology

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

6.3 Pharmacodynamic Procedures

Detailed ophthalmic examination will be used to evaluate the pharmacodynamic effects of PP-001 on the eye. All procedures should be performed at the times outlined in the Time and Events table (Table 1 and Table 2) and will be performed on both eyes in order to provide a non-treated comparison. Further details on the conduct of the ophthalmic examinations can be found in the SRM.

6.3.1 Best Corrected Visual Acuity

Best corrected visual acuity will be measured in both eyes using an Early Treatment Diabetic Retinopathy Study (ETDRS) chart. Subjects will be asked to read the smallest letters they can from a chart.

6.3.2 Visual Field Measurement

A 30° visual field measurement will be conducted using computerised perimetry. Subjects will be asked to identify when they can see flashing lights at the periphery of their vision whilst staring straight ahead. The lights will gradually move towards the centre of the screen, so identifying the extent of the subject's peripheral vision.

6.3.3 Intraocular Pressure

Intraocular pressure will be measured using Goldmann contact tonometry. This involves pressing the tonometer prism against the cornea after topical anaesthesia in order to determine the intraocular pressure.

6.3.4 Slit Lamp Examination

A slit lamp will be used to examine the conjunctiva, cornea and 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). Conjunctival hyperemia will be scored using a standardized photographic scale derived from McMonnies

grading (0-5) (McMonnies & Chapman-Davies 1987) in cohorts 1-3. In cohort 4, conjunctival hyperemia will be scored according to the scale proposed by Efron et al. 1998, see chapter 6.3.9.

6.3.5 Dilated Fundoscopy

Examination of the fundus (retina) will be carried out as part of the eye exam following dilation of the subject's pupils. Slit lamp biomicroscopy of the fundus will be performed as part of this procedure.

6.3.6 Fundus Photography

While the subject's pupils are dilated the eye, retina, retinal vasculature, optic disc, macula and posterior pole will be photographed using a retinal camera. Vitreous haze will also be documented if present.

6.3.7 Amsler Grid

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

6.3.8 Ocular surface disease index (OSDI)

Symptoms of dry eye will be assessed using the Ocular Surface Disease Index (OSDI). The questionnaire that underlies the OSDI is specifically designed for patients with ocular surface disease and asks patients about the frequency of specific symptoms and their impact on vision-related functioning.

6.3.9 Assessment of conjunctival hyperemia

Conjunctival hyperemia will be assessed by the investigator during slit lamp examination according to the scale proposed by Efron et al. 1998:

(0) = None

(1) = Trace

(2) = Mild

(3) = Moderate

(4) = Severe

6.3.10 Tear film osmolarity

Tear film osmolarity will be measured non-invasive with a commercially available instrument (TearLab®, OcuSens Inc, San Diego, USA). The TearLab® technology uses an approach that concentrates laboratory functions on a single chip that requires less than 50 nL of tear fluid in order

to measure tear osmolarity. The system uses a handheld pen on which the ophthalmologist places the noninvasive laboratory chip test card. Then the tear sample is collected by pressing the tip of the pen towards the conjunctiva adjacent to the lower lid margin. The collection of the tear sample takes usually less than 30 seconds and is painless for the subject.

6.3.11 Corneal fluorescein staining

Minims-Fluorescein Sodium 2.0% eye drops will be used to detect corneal epithelial defects. As grading scale for corneal damage, the NEI/Industry Workshop guidelines will be used (Lemp 1995). The cornea will be divided into five sectors (central, superior, inferior, nasal and temporal), each of which is scored on a scale of 0–3, whereas 0 means no staining and 3 means maximum staining, with a maximal score of 15.

6.3.12 Tear film break up time (BUT)

Tear break up time will be measured following the guidelines published in the Report of the International Dry Eye Work Shop (DEWS) 2007. Briefly, Minims-Fluorescein Sodium 2.0% eye drops are applied in the conjunctival sac of the eye. The patient is instructed to blink naturally without squeezing several times to distribute the fluorescein. Within 10 - 30 seconds after fluorescein instillation, the patient is asked to stare straight ahead without blinking, until told otherwise. By the means of a stopwatch the time between last complete blink and first appearance of a dry spot is recorded. Once breakup of the tear film is observed, the patient will be instructed to blink freely.

6.3.13 Conjunctival staining using lissamine green

Lissamine green (LG, EasyOpht, Italy) will be used to detect conjunctival defects. Before placing the strip in the lower fornix of the eye, a drop of sterile saline must be added to the strip. As grading scale for conjunctival damage, the NEI/Industry Workshop guidelines will be used (Lemp 1995). Both nasally and temporally, the conjunctiva is divided into a superior paralimbal area, an inferior paralimbal area and a peripheral area with a grading scale of 0–3, whereas 0 means no staining and 3 means maximum staining, with a maximal score of 9 for the nasal and temporal conjunctiva.

6.4 Prior and Concomitant Medications

Regular use of any ocular agents within 60 days prior to Day 0 will be assessed. 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 a treatment for an AE. The minimum requirement is that drug name, indication and the stop and start dates of administration are to be recorded.

6.4.1 Prior Medications

A medication history will be taken at Screening. Regular use of any ocular agents within 60 days prior to Day 0 will be assessed. All non-ocular medications taken within 1 week before Day 0 will be entered into the eCRF.

6.4.2 Concomitant Medication

All concomitant medications taken during the study will be recorded in the subject's eCRF. All concomitant medications taken during the outpatient phase will be recorded by the subject in a diary card and transcribed by site staff into the eCRF.

In cohort 4, subjects will be handed out a bottle of topical lubricants (Genteal HA, Laboratoires Thea, France) as standard of care treatment for the control eye as needed. Subjects will be instructed to document instillation dates and times for Genteal HA eye drops in a diary card and entries will be transcribed by site staff into the eCRF.

6.5 Prohibited Medications

The following medications are prohibited during this study and for at least five half-lives prior to Day 0:

- Local or systemic biologicals (i.e., tumour necrosis factor-blockers, B cell-blockers, cytokines, cytokine-blockers, receptor antagonists)
- Cyclophosphamide or chlorambucil
- Immunosuppressive, immunomodulatory or steroid treatment
- Any anticoagulant or thrombocyte aggregation inhibiting agent (marcumar, warfarin, heparin, enoxaparin, apixaban, rivaroxaban, pentosanpolysulfate, dabigatran, aspirin and others)
- Any systemic antibiotic treatment

6.6 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.

6.7 Total Blood Volume Collected

Subjects in cohorts 1-3 will have approx. 50 mL of blood collected for safety and pharmacokinetic evaluations during the study. Subjects in cohort 4 will have approx. 46 ml of blood collected for safety evaluations during the study.

6.8 Discontinuation from Treatment or Study

Subjects are free to withdraw from the study at any time for any reason. Subjects may be withdrawn from the study at the discretion of the Investigator. Once a subject has been withdrawn from the study, they may not be re-entered. Subjects who withdraw or who are withdrawn from the study before day 21 will be replaced. Subjects who are withdrawn due to AEs will not be replaced. If a subject is discontinued from treatment or from the study, the reason for discontinuation will be collected in the eCRF.

If a subject is prematurely withdrawn from study treatment, the Investigator should make every effort to retain the subject in the study and perform all procedures scheduled for the follow-up. Any subject withdrawn from treatment due to an 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.

6.8.1 Discontinuation from Study

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

- Withdrawal of consent by subject (if provided, the reason should be specified in the eCRF)
- Lost to follow-up
- Death
- Physician decision (i.e., assessment that it is not in the subject's best interest to continue, or another reason; the reason should be specified in the eCRF)
- The Sponsor may terminate the study at any time

6.8.2 Individual Stopping Criteria

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

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

Subjects 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 subject may also withdraw from the study at any time at their own request.

If a subject is prematurely withdrawn from study treatment, the Investigator should make every effort to retain the subject in the study and to perform all procedures scheduled for the follow-up visit. Any subject 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.

6.8.3 Study Stopping Criteria

Dosing of further subjects will be halted if the following criterion is met:

- Severe AEs classified as being possibly, probably or definitely study-drug related or potential major safety concerns as identified by the Investigator after consultation with the DSMB are reported in more than 50% of subjects in the same cohort

Dosing will be stopped or the dose decreased if:

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

6.8.4 Lost to Follow-up

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

6.9 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 document the reasons for termination. The Sponsor will ensure that the relevant regulatory agencies and main research ethics committees are notified

6.10 Contraceptive measures

Women of childbearing potential and 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 and female subjects 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 becoming pregnant or fathering a child in the 3 months following the last study drug administration. Male subjects 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 (oestrogen 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 subjects 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.

Female subjects of childbearing potential must perform a negative urine pregnancy test prior to the first instillation of PP-001. In cohorts 1-3, an additional urine pregnancy tests will be performed during the safety visit on Study Day 8 and Study Day 28. In cohort 4, urine pregnancy tests will be performed at screening, on Study day 0 and on Study Day 20.

7. ADVERSE EVENTS

An AE is any untoward medical occurrence in a patient or clinical investigation subject 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 IP, whether or not related to the IP.

Any pre-existing conditions or signs and/or symptoms present in a subject 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.

Subjects 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, subjects will be encouraged to report any AEs spontaneously. Subjects will also record any AEs occurring during the outpatient phase in a subject diary card. Any subject 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 for any SAEs. Where appropriate, medical tests and examinations may be performed to ensure that an AE has fully resolved.

Adverse events and SAEs will be monitored throughout the study from the time a subject provides consent through to the final 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 subject'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 subject's eCRF.

Each AE or SAE reported will be assessed for severity and the date and time of onset (if available), 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.

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 subject is still able to function.

Severe: A 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 can readily be explained by factors not involving the study drug and a temporal relationship with the study drug does not exist.

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

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

Definitely Related The event follows a reasonable temporal sequence from administration of the study drug, follows a known or suspected response pattern to the study drug, was confirmed by improvement upon stopping the study drug

(dechallenge) and reappears upon repeated exposure (rechallenge). Note: this is not to be construed as requiring re-exposure of the subject, however, a category of definitely related can only be used when recurrence is 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 subject hospitalisation or prolongation of existing hospitalisation
- 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 hospitalisation but may jeopardise the subject 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 hospitalisation or development of drug dependency or drug abuse.

All SAEs for subjects 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).

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 the Clinical Trials Coordination Centre, Medical University of Vienna. 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 Clinical Trials Coordination Centre, Medical University of Vienna. 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

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

Clinical Trials Coordination Centre, Medical University of Vienna:
Phone: +43 (0)1 40160 25176

Panoptes Pharma:

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 (subject becomes pregnant while taking study drug)
    - Subjects who are pregnant at Screening are not permitted to take part in this study; however, Panoptes Pharma GesmbH or their representative must be notified of any subjects that become pregnant while participating in this study (or the partner of a male subject). 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 subject that occurs during this study to Panoptes Pharma GesmbH or their representative.
- Lactation exposure (subject is taking study drug while nursing an infant)
- Accidental exposure (someone other than the study subject is exposed to study drug)
- Overdose (subject receives more than the prescribed dose of study drug within a given timeframe)
- Other medication errors that potentially places subjects at a greater risk of harm than is previously known or recognised (e.g., study drug is administered by an incorrect route)

8. DRUG SUPPLIES

8.1 PP-001

PP-001 is formulated as sterile, ophthalmic formulation (eye drop formulation) at three different strengths (3.0, 1.5 and 0.5 mg/ml). Sodium chloride, sodium hydroxide, hydrochloric acid, human serum albumin (HSA) and water for injection are added as excipients. The formulation does not contain preservative agents. Final dosage forms were prepared by diluting a concentrate formulation (5.0 mg/ml) of the highest technically feasible PP-001 concentration in this composition with vehicle solution. As primary package material, sterile 10 ml LDPE dropper bottles are used. Filling volume of each bottle is 3 ml. An overview on the composition of the formulation and a description of the function of the ingredients is given below in Table 5.

Table 5: Qualitative composition of PP-001 eye drop formulation

Component	Function	Reference to Quality Standards
PP-001	Active ingredient	In-house specification
Human serum albumin*	Solubilizing agent	Ph. Eur.
Sodium chloride	Tonicity adjustment	Ph. Eur.
Sodium hydroxide	pH adjustment, deprotonation, solubilizing agent	Ph. Eur.
Hydrochloric acid	pH adjustment	Ph. Eur.
Water for injection	Solvent	Ph. Eur.

*Albunorm 20%®; diluted to 5% final concentration

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 subjects 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 bottles 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.

The unit of accountability will be one bottle of eye drops.

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

A comparison will be made between the cohorts with regard to safety and tolerability.

9.2 Sample Size Determination

Twenty-four healthy female or male subjects will be enrolled in cohorts 1-3. Twenty-one subjects will be enrolled in cohort 4. No power calculations have been 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 subjects regardless of whether or not the subject received study drug.

9.3.2 Per-protocol Analysis Set

The Per-protocol Analysis Set will consist of all ITT Analysis Set subjects 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 subjects who receive any amount of study drug. All safety analyses will be conducted in this population.

9.3.4 Pharmacokinetic Analysis Set

All subjects in cohorts 1-3 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 parameters (i.e., changes in clinical signs and symptoms from physical exam, changes in clinical laboratory parameters, vital signs and AEs).

9.4.2 Pharmacokinetic Analysis Variables

The concentration of PP-001 in plasma at predose, postdose (30 min and 1h ± 5 minutes after dosing), day 8 and day 19 (30 min ± 5 minutes after last dosing of the day) will be determined (cohorts 1-3 only).

9.5 Demographic and Baseline Characteristics

Enrolment, protocol deviations and discontinuations from the study drug and the study will be summarised. Demographics (age, race, ethnicity and sex), medical and surgical history and study drug administration will also be summarised 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 treatment-emergent AEs (TEAEs). A TEAE 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 subjects 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 summarised at each study visit and the worst overall post-baseline value will be provided. The number and percent of subjects with treatment-emergent values with potential clinical significance will be tabulated.

Descriptive statistics of laboratory parameters and the change from baseline for each scheduled evaluation will be summarised at each study visit. The number and percent of subjects with treatment-emergent values of potential clinical significance will be tabulated by parameter.

9.7 Pharmacokinetic Analyses

The concentration of PP-001 in plasma will be measured in blood samples from subjects of cohorts 1-3, taken at pre-dosing, 30 min and 1h post-dosing and on day 8 and day 19 at 30 min after the last administration of the day. The PP-001 concentrations in plasma will be listed, graphed, and summarized by time point, day and treatment group.
Descriptive statistics for the PK parameters will include mean, standard deviation, coefficient of

variation, geometric mean, CV% geometric mean, median, min and max. When a geometric mean will be presented, it will be stated as such.

9.8 Handling of Missing Data

Missing values will not be imputed.

9.9 Interim Analysis

Cohorts 1 to 3 will be performed in dose ascending order. On the first two study days in Part I of each cohort, one subject will be dosed per day. On the third study day up to two subjects can be dosed per day. On the following study day(s) up to 4 subjects can be dosed per day. Randomization will be performed in two blocks (3:1, PP-001 vs. placebo) for each cohort. Part II will start at least 7 days after the last subject has been dosed in Part I and the Principal Investigator and the sponsor decide whether or not to continue dosing the cohort in Part II. The DSMB will decide if the safety and tolerability demonstrated in Parts I and II of the previous cohort warrant continuing the study at the next highest dose.

10. STUDY MONITORING

10.1 Clinical Monitoring

All aspects of the study will be carefully monitored by the Sponsor's authorised 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 Investigator.

Frequent communication between the study site and the Sponsor is essential to ensure that the subject 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 Data Safety 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 DSMB after each cohort 1-3 in written form and throughout the study based on the above. For details please refer to the DSMB charter.

11. INDEPENDENT ETHICS COMMITTEE APPROVAL

The Investigator agrees to provide the Independent Ethics Committee (IEC) with all appropriate material, including a copy of the informed consent form. The study will not be initiated until the Investigator obtains written approval of the research plan (protocol) and the informed consent form from the appropriate IEC and copies of these approval 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 and current amendments, the Declaration of Helsinki (revised version of Fortaleza, Brazil 2013), GMP, GCP and the current national regulations and guidelines. The study will be approved by both the local ethics committee and regulatory authority prior to first subject first visit.

13. INFORMED CONSENT

The ICH has issued guidelines to provide protection for human subjects 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 subject 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 subject in non-technical terms. Subjects (or their legally authorised representative) will be required to read, voluntarily sign, and date an informed consent form summarising the discussion at Screening, and will be assured that they may withdraw from the study at any time without jeopardising their medical care.

Subjects will sign and date one copy of the informed consent form, which will be photocopied. The copy will be retained by the subject 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 subject 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 subjects' hospital notes, recorded on source data forms, or in the subject diary card, 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., Visual field tests, laboratory results) will be included in the source documentation. Any results outside the normal range should be designated by the Investigator or designee as "CS" or "NCS".

15.2 Data Protection

The Investigator and his/her staff will be required to manage subject 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 and Regulation on Data Privacy concerning the processing and use of subjects' personal data. For the purpose of data privacy legislation, Panoptes Pharma GesmbH will be the data controller.

After subjects 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.

Subjects 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 subject. 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 executed at the clinical site listed below.

Assoc. Prof. Priv.-Doz. Dr. Gerhard Garhöfer
Universitätsklinik für Klinische Pharmakologie, AKH Wien
Währinger Gürtel 18-20
1090 Wien
Austria

Bioanalysis of plasma samples will be performed at the following analytical laboratory:

A&M Labor GmbH
Kopernikusstr. 25
50126 Bergheim
Germany
Managing directors: Dr. Axel Römer, Dr. Tobias Klaassen
Phone: +49 (0)2271 4787 0 Fax: +49 (0)2271 4787 44

Study Management:

Clinical Trials Coordination Center
Medizinische Universität Wien
Koordinationszentrum für Klinische Studien
Währinger Straße 25a, OG 1, 1090 Wien
Phone: +43 (0)1 40160 25176

SOURCIA GmbH
Pasinger Strasse 58
82166 Gräfelfing
Germany
Phone: +49 (0)89 89 55 807-0

17. TERMINATION OF STUDY

The Sponsor reserves the right to discontinue this study at any time.

18. FINANCING AND INSURANCE

The costs necessary to perform the study will be agreed with the 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, this 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 recognised 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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Investigators Brochure, current version

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21. APPENDICES

21.1 Appendix 1: Clinical Laboratory Tests

Blood and urine samples for the following parameters will be sent to a local laboratory for testing except for alcohol testing and drug screen. Alcohol will be tested using a breathalyzer at the clinical site. Drug Screen will be performed using a dipstick test at the clinical site.

Haematology

- Coagulation panel (including prothrombin time with international normalised 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
- Creatine phospho-kinase
- Total bilirubin
- Direct bilirubin (in case total bilirubin is >2)
- Uric acid
- Albumin
- Total protein

Urinalysis

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

Other tests

- drug screen including alcohol (screening visit, predose in each session)
- HIV, Hepatitis B and hepatitis C Test at screening

21.2 Appendix 2: Values of potential concerns

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