Statistische Analysen und Monitoring GmbH

Clinical Study Report

Title:	**Prospective, Controlled, Randomized, Investigator-masked, Multicenter, Phase III Trial to demonstrate the Efficacy and Safety of Brimonidine UD**
IMP:	Brimonidine UD
Indication:	Elevated intraocular pressure
Sponsor:	Pharma Stulln GmbH
Project code:	PSt012015, EudraCT-No.: 2015-001489-24
Phase:	III
First patient in:	March 9th 2016
Last patient out:	October 31st 2016
Early Study Termination:	November 24th 2016
Coordinating investigator:	Dr. Jürgen Mende
Author:	Dr. Dieter Werdier

This study was performed in compliance with Good Clinical Practice.

Final Version: 31st March 2017

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1. Synopsis

Study title	Prospective, Controlled, Randomized, Investigator-masked, Multicenter, Phase III Trial to demonstrate the Efficacy and Safety of Brimonidine UD
Clinical trial reference code	PSt012015
EudraCT No	2015-001489-24
Sponsor	Pharma Stulln GmbH Werksstraße 3 92551 Stulln Germany Phone: +49 9435 / 3008-0 Fax: +49 9435 / 3008-99
Coordinating investigator	Dr. med. Jürgen Mende Reisholzer Straße 33 40231 Düsseldorf Germany Tel.: +49 211 / 2292219 Fax: +49 211 / 2293322
Test drug	Brimonidine UD
Active ingredient	Brimonidine
Pharmaceutical form	Eye drops, solution containing 2 mg/ml brimonidine tartrate, equivalent to 1.3 mg/ml brimonidine
Comparator drug	Alphagan®
Active ingredient	Brimonidine
Pharmaceutical form	Eye drops, solution containing 2 mg/ml brimonidine tartrate, equivalent to 1.3 mg/ml brimonidine
Objective	Proof of efficacy of the test drug concerning the reduction of an elevated intraocular pressure (IOP)
Indication	Elevated intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension
Trial design	Prospective, controlled, randomized, investigator masked, multicenter trial
Phase	III
Number of trial sites	6
Number of patients	8
Inclusion criteria	1. Male patients and female patients who use an effective contraceptive method or are out of child bearing potential 2. Patient is at least 18 years old 3. Patient suffers from open angle glaucoma or from ocular hypertension

1. Synopsis (continued)

Inclusion criteria (continued)	4. The medical condition named in 3 has not been treated pharmacologically before or the patient has undergone a 7 day wash out phase. 5. IOP ≥ 22 mmHg and ≤ 30 mmHg 6. The patient has been informed about the clinical trial and signed the informed consent form.
Exclusion and withdrawal criteria	1. Eye diseases (except for the ones named in inclusion criterion 3) which require treatment 2. IOP > 30 mmHg 3. Ocular irritations (e.g. edema, redness) at screening 4. Ocular inflammation or present effects of previous eye diseases which could influence the results of IOP measurements 5. Other glaucoma or ocular hypertension treatment during the trial 6. Eye surgery 3 month or less prior to screening 7. Concomitant therapy with monoamine oxidase (MAO) inhibitors or with antidepressants which affect noradrenergic transmission (e.g. tricyclic antidepressants and mianserin) 8. Severe or unstable and uncontrolled cardiovascular conditions 9. Severe systemic concomitant diseases 10. Liver or kidney diseases 11. Scheduled major surgeries 12. Enrolment in another clinical trial within the last 4 weeks or during enrolment in this trial 13. Known hypersensitivity to the active ingredient or any excipient of the IMPs 14. Women: pregnancy or lactation 15. Previous or current alcohol or drug abuse 16. Mental or emotional instability that might jeopardize the validity of the informed consent or the compliance with the trial procedures 17. Unreliability or lack of cooperation 18. Other reasons why, in the opinion of the investigator, the patients should not participate in the trial
Duration of the clinical period of the trial	Planned duration: 6 months Actual duration: 7 months and 22 days
	Recruitment of the first patient: 9th March 2016 Recruitment of the last patient: 6th October 2016 Last visit of the last patient: 31st October 2016
Trial duration for each patient	22 days
Duration of the therapy	21 days (= 42 applications from day 0 until day 21)

1. Synopsis (continued)

Trial schedule	Visit 1 (day 0) = screening: Written informed consent, screening: anamnesis, IOP measurement by contact tonometry, randomization, dispensing of IMP and subject diary part 1 Visit 2 (day 14) = control: IOP measurement, ophthalmological assessment, review of the subject diary entries part 1 and handing out of part 2 Visit 3 (day 21) = completion: IOP measurement, ophthalmological assessment, review of the subject diary entries part 2, efficacy, safety and usability assessment of the IMP, return and review of the used and unused IMP Drop-out visit Like visit 3, investigator asked about the reason for drop out
Efficacy parameters	The primary efficacy endpoint was the non-inferiority of Brimonidine UD for treatment of an elevated IOP in the range of 22 – 30 mmHg in comparison to Alphagan®. Thus, the IOP was the primary variable under consideration.
Safety parameters	The secondary endpoint was the superiority of Brimonidine UD over Alphagan® regarding side effects. Symptoms of side effects and adverse events were analysed as safety parameters.
Statistical modelling and methods, sample size	Modelling Let the IOP distributions of the two therapy groups "standard therapy" and "test therapy" be realisations of normal distributed random variables X(standard, start), X(standard, end), X(test, start) and X(test, end) at the start and at the end of the study, than the differences D(standard) = X(standard, start) – X(standard, end) and D(test) = X(test, start) – X(test, end) of these variables are normally distributed as well. Let $\mu_{standard} = E(D_{standard})$ and $\mu_{test} = E(D_{test})$ be the corresponding expected values of these differences with equal variances $\sigma_{standard}^2 = \sigma_{test}^2$. To analyse the non-inferiority of the efficacy of the test therapy compared to the efficacy of the standard therapy, the hypothesis H_{01}: $\mu_{standard} - \mu_{test} \geq 1.9$ mmHg was tested against H_{11}: $\mu_{standard} - \mu_{test} < 1.9$ mmHg by using a one-sided *t*-test for independent samples with a type I error rate of α = 0,05 and a type II error rate of ß = 0,05, for a clinically relevant difference d = 2 mmHg with a standard deviation of s = 2.5 mmHg, estimated from former trials. Sample Size For the above mentioned decision criteria (see Cohen, 1977) n = 35 patients were necessary per group for the analysis. Assuming a drop-out rate of 12.5 %, 40 patients had to be randomized into each of the therapy groups.

1. Synopsis (continued)

Summary	The clinical part of the trial was conducted at 6 trial sites between 3rd March 2016 and 31st October 2016. 8 patients were recruited for the trial at 3 trial sites. Overall 7 patients completed the trial regularly. 1 patient terminated the participation prematurely because of an adverse drug reaction (ADR). Altogether 3 ADR occurred in 2 patients. Serious adverse events (SAE) / serious adverse drug reactions (SADR) did not occur. Due to an insufficient recruitment of patients, the trial was terminated on November 24th 2016 prematurely. A conclusive evaluation is not possible due to the insufficient number of patients.

2. List of Abbreviations

Abbreviation	Meaning
α	Type I error rate
ADR	Adverse drug reaction
AE	Adverse event
ars®	Investigator computer interface (German: Arzt-Rechner-Schnittstelle)
β	Type II error rate
BAC	Benzalkonium chloride
BfArM	Federal institute for drugs and medical devices (German: Bundesinstitut für Arzneimittel und Medizinprodukte)
CNS	Central nervous system
CRA	Clinical research associate
CRF	Case report form
CRO	Contract research organization
d	Difference
eCRF	Electronic case report form
EDC	Electronical data capture
EDP	Electronical data processing
e.g.	For example (Latin: exempli gratia)
etc.	Et cetera
GCP	Good clinical practice
Hg	Hydrargyrum / mercury
ICF	Informed consent form
i.e.	That is (to say) (Latin: id est)
IEC	Independent ethics committee
IMP	Investigational medicinal product
IMPD	Investigational medicinal product dossier
IOP	Intraocular pressure
ITT	Intent to treat
MAO	Monoamine oxidase
μ	Mean

Abbreviation	Meaning
mm	Millimetre
n	Sample size
p	Probability
PI	Principle Investigator
PP	Per protocol
RDE	Remote data entry
s	Standard deviation
SA	Safety Analysis
SADR	Serious adverse drug reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SI	Sub Investigator
SOP	Standard operating procedure
UD	Unit dose
vs.	Versus
(w/v)	Weight per volume
WHO	World Health Organization
WHO-UMC	World Health Organization Uppsala Monitoring Centre

3. Ethics and Regulations

3.1. Ethics Committee

All trial relevant documents, including protocol, appendices, subject diary and CRF, were submitted to the responsible ethics committee of the North Rhine medical council (Ärztekammer Nordrhein) by means of the letter dated 30th September 2015. By means of the letter dated 19th November 2015 the ethics committee stated to not give rise to any ethical and legal reservations regarding the conduct of the trial.

The subsequent amendments of the trial protocol version 1.0 (Amendment 1) were submitted by means of the letter dated 23rd November 2015 to the ethics committee of the North Rhine medical council. On 14th December 2015 a consenting appraisal of the ethics committee arrived.

The subsequent amendments of the trial protocol version 2.0 (Amendment 2) were submitted by means of the letter dated 29th June 2016 to the ethics committee of the North Rhine medical council. The corresponding consenting appraisal of the ethics committee arrived on 20th July 2016.

On 2nd December 2016 the ethics committee of the North Rhine medical council confirmed the receipt of the letter concerning the premature termination of the trial.

For a list of ethics committees involved in the trial please note appendix 0.

3.2. Higher Federal Authority

The application documents for the conduct of the clinical trial were submitted to the federal institute for drugs and medical devices (German: BfArM, Bundesinstitut für Arzneimittel und Medizinprodukte, Kurt-Georg-Kiesinger-Allee 3, 53175 Bonn, Germany) on 21st July 2015. The approval of the conduct of the clinical trial was granted on 16th September 2015 by the BfArM.

On 24th November 2016 the BfArM was informed by telephone about the premature termination of the clinical trial due to the insufficient recruitment of patients. On 5th December 2016 the BfArM confirmed the termination of the trial in writing.

3.3. Ethical Conduct of the Trial

The trial was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

3.4. Patient Information and Consent

Patients complying with the selection criteria were informed verbally and in writing about the nature, objectives, risks, and impact of the trial as showed in appendix 0 of the report. The appendix 0 also contains the text from the informed consent form (ICF). The ICF was signed by the patient prior to enrolment. The dated and signed ICF remained for data protection reasons with the investigator and was available at all times for the verification of the duly executed informed consent. The patient was provided with a copy of the ICF.

The identification of patients and allocation of individual data was prevented by solely using patient numbers for the patient identification. It was prohibited to submit further patient identification information outside the trial site. Lists for the identification of individual patients exclusively remained at the trial site.

The patients were informed verbally and in writing that all data collected should remain strictly confidential and would be processed and analysed solely for the scientific purpose of this trial.

4. Investigators and Trial Administrative Structure

Coordinating Investigator	Dr. med. Jürgen Mende Reisholzer Straße 33 40231 Düsseldorf, Germany Tel.: +49 211 / 2292219 Fax: +49 211 / 2293322
Investigator	Dr. Stefanie Ameye Kaiserswerther Markt 20, 40489 Düsseldorf, Germany
Investigator	Prof. Dr. Chris Lohmann Klinikum Rechts der Isar, Technische Universität München Ismaninger Straße 22 81675 München, Germany
Investigator	Dr. Tobias Neuhann Augenärzte an der Oper Residenzstraße 9 80333 München, Germany
Investigator	Dr. Matthias Klamann Charité Universitätsmedizin Berlin Augustenburger Platz 1 13353 Berlin, Germany
Investigator	Dr. Dr. Katrin Lorenz Universitätsmedizin, Johannes Gutenberg-Universität Mainz Langenbeckstrasse 1 55131 Mainz, Germany
Sponsor	Pharma Stulln GmbH Werksstraße 3 92551 Stulln, Germany Tel.: +49 9435 / 3008-0 Fax: +49 9435 / 3008-99
Project managers at the sponsor	Dr. Karl Luschmann, CEO, Qualified Person; Dr. Michaela Bergmann, Pharmacovigilance Manager Pharma Stulln GmbH Werksstraße 3 92551 Stulln, Germany Tel.: +49 9435 / 3008-170 / -142 Fax: +49 9435 / 3008-99
Biostatistician and responsible CRO	Dr. Dieter Werdier, CEO SAM®, Statistische Analysen und Monitoring GmbH Am Gut Wolf 3 52070 Aachen, Germany Tel.: +49 241 / 888 2 103 Fax: +49 241 / 888 2 100
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5. Introduction

Glaucoma is a group of diseases of the eye that leads to a degeneration of retinal ganglion cells and to the excavation of the optical nerve head, which results in progressive vision field loss. Glaucoma is a common cause of blindness in industrialized countries. In Germany, about 800,000 to 900,000 patients suffer from glaucoma and the number of patients with undiagnosed glaucoma is estimated to be the same. The prevalence rises with age, from approximately 2.4 % in individuals older than 40 years to more than 7 % in individuals older than 75 years (Dietlein et al. 2009). Increased intraocular pressure (IOP) is an important risk factor (Kass et al. 2002) and is observed in most glaucoma patients. Open angle glaucoma, caused by insufficient drainage of aqueous humor through the trabecular meshwork, is the most prevalent form of glaucoma (Congdon et al. 1992, Bonomi et al. 2000). The glaucoma induced neuropathy is irreversible. The only therapies available focus on lowering the elevated IOP, in most cases by application of IOP lowering drugs. When pharmacological treatment is not applicable, surgical procedures, like trabeculectomy, are performed (Kuehn et al. 2005, Sambhara D. and Aref A. A. 2014).

Brimonidine is an α2-adrenergic receptor agonist. It decreases the production of aqueous humor and induces increased drainage (Toris C. B. et al. 1995). Topical application of 0.2 % brimonidine into the eye effectively lowers the IOP (Schuman J.S. et al. 1997, Toris C. B. et al. 1995). Brimonidine eye drops are marketed in Germany since 1998 for the treatment of open angle glaucoma and ocular hypertension. The affinity of brimonidine for the α2-adrenergic receptor is 1,000 times higher than the affinity for the α1-adrenergic receptor (Burke J. and Schwarz M. 1996). Lachkar et al. studied the effects of brimonidine on hemodynamics in patients who applied 0.2 % brimonidine eye drops twice daily for two weeks. No changes in the hemodynamic parameters were observed (Lachkar et al. 1998). The most common side effects observed with the use of brimonidine eye drops are oral dryness, ocular hyperaemia and ocular burning / stinging.

The brimonidine eye drops currently marketed contain benzalkonium chloride (BAC). BAC is a commonly used preservative in ophthalmic solutions. It is a quaternary ammonium compound, which acts as a detergent to disrupt the lipid membrane of cells, thus killing microorganisms. However, BAC also disrupts the lipid layer of the tear film, which can lead to dry eyes (Rosin and Bell, 2013). Significant cytotoxic effects of BAC have been demonstrated *in vitro* and *in vivo*. These effects are used to explain irritations and damages observed in the eyes of patients using eye drops containing BAC. This is critical for glaucoma patients who have to continuously use eye drops for the treatment of their condition. Long-term use of BAC is correlated with toxic and inflammatory processes in the eye, in particular conjunctivitis and blepharitis. These processes can result in subconjunctival fibrosis, which again decreases chances for successful trabeculectomy. Also, the incidence rates of endothelial damage, epithelial edema, and bullous keratopathy are increased in glaucoma patients (Noecker, 2001).

The investigational medicinal product (IMP) in this trial, Brimonidine UD, are eye drops with 1.3 % (w/v) brimonidine and without BAC. Brimonidine UD is supplied in unit dose vials, which makes the addition of BAC unnecessary. The hypothesis is Brimonidine UD to be a non-inferior substitute for Alphagan® eye drops with 1.3 % (w/v) brimonidine as the active ingredient and with BAC as a preservative in the treatment of elevat-

ed IOP. We expect Brimonidine UD to cause fewer side effects than Alphagan®, which would benefit the patients.

6. Objectives of the Trial

The objective of this trial is to demonstrate the efficacy and safety of Brimonidine UD in the reduction of an elevated IOP that can be treated by monotherapy with eye drops containing 1.3 mg/ml brimonidine as the active ingredient.

6.1. Primary Efficacy Endpoint

The primary efficacy endpoint is non-inferiority of Brimonidine UD in the reduction of elevated IOP in the range of 22 – 30 mmHg as compared to Alphagan®.

6.2. Safety Endpoint

The safety endpoint is superiority of Brimonidine UD vs. Alphagan® regarding side effects.

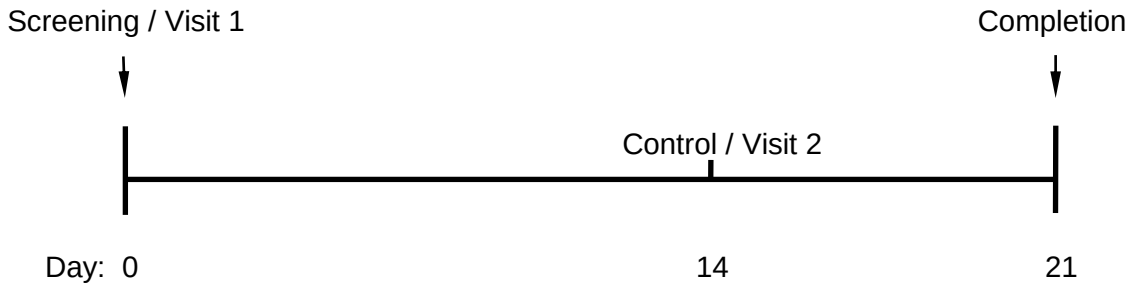
7. Investigational Plan

7.1. Design of the Trial

This prospective, controlled, randomized, investigator-masked, multicenter phase III trial was designed to demonstrate the efficacy and safety of Brimonidine UD. Patients were randomly assigned to the treatment group or the control group. Patients assigned to the treatment group received a monotherapy with Brimonidine UD and patients assigned to the control group received a monotherapy with Alphagan®. The IOP was measured in both eyes. Drop-outs were not replaced.

7.2. Duration of the Trial

The clinical period of the trial lasted 8 months. Each patient was treated 21 days. Depending on the randomization the patient took either the test drug Brimonidine UD or the active comparator drug Alphagan® twice per day.



7.3. Conduct of the Trial

For a complete overview of the schedule of assessments see 7.4.

Visit 1 (day 0) = Screening

The patient was informed about the trial objectives and about the risks and benefits he could expect for himself in a discussion with the investigator and by reading the information leaflet. The patient had to give his written informed consent before screening started.

According to the selection criteria the eligibility of the patient was evaluated. Demographic data on age, sex, weight, and height was collected, as well as anamnestic data on onset and therapy of the patients open angle glaucoma / ocular hypertension, known allergies and drug intolerances, previous and concomitant diseases and medications.

The following signs and symptoms of ocular irritation were assessed and the results were documented: conjunctival redness, eyelid redness, eyelid edema, burning / stinging of the eye, pruritus of the eye, foreign body sensation in the eye and blurred vision.

The IOP was measured by contact tonometry.

The patient was then randomized and received the IMP in a sealed box, which was not to be opened at the trial site. The patient was instructed to use the IMP according to

the specifications stated in chapter 9.1. The patient used the IMP until day 21. The last application on day 21 took place approximately two hours before the final examination.

During the trial, the patient was not to use any medications other than the IMP for the treatment of the open angle glaucoma / elevated intraocular pressure.

The patient also received a paper subject diary for the daily documentation of the treatments and ocular irritations until the next visit 2 (for more details see subject diary part 1 in appendix 20.3).

Visit 2 (day 14) = Control

The IOP was measured again. Patients meeting one of the withdrawal criteria had to be withdrawn from the trial immediately and had to receive further treatment for their open angle glaucoma / elevated intraocular pressure. Because the IOP changes during the day, the measurement of the IOP should take place at the same time as in visit 1. Signs and symptoms of ocular irritation were assessed and documented again: conjunctival redness, eyelid redness, eyelid edema, burning / stinging of the eye, pruritus of the eye, foreign body sensation in the eye and blurred vision. The patient handed the subject diary documentation for the first 14 days (day 0 until day 14) to the investigator, in order for the investigator to enter the data into the RDE system.

Changes in concomitant medications and diseases were documented as well as adverse events.

The patient received the second part of the paper patient diary until visit 3 (see subject diary part 2 in appendix 20.3).

Visit 3 (day 21) = Completion

In visit 3 procedures were the same as in visit 2. In addition, the investigator and the patient each assessed the overall efficacy and safety of the IMP. The patient also assessed the usability of the IMP. The patient handed the subject diary documentation for the days 14 to 21 to the investigator, in order for the investigator to complete the data in the RDE system.

At the end of the visit, the patient returned all the previously received primary and secondary IMP packs.

Drop-out Visit

The patient that dropped out was upon consent invited to a drop-out visit for a final examination. The procedures of this visit were the same as of visit 3. In addition, the investigator asked about the reason for the patient to drop out. The reason was documented. The visit did not take place later than the next scheduled visit.

After the patient terminated the participation in the trial, the investigator made sure to supply adequate treatment for the open angle glaucoma or ocular hypertension the patient suffered from.

7.4. Schedule of Assessments

Visit	**1**	**2**	**3***
Day	**0**	**14**	**21**
Examination	**Screening**	**Control**	**Completion**
Informed Consent	x		
Selection criteria	x	x	x
Demographic data	x		
Anamnesis	x		
Concomitant diseases and medications	x	x	x
<u>IMP</u> Dispensing Return	 x		 x
<u>Efficacy</u> IOP measurement Overall assessment (Investigator and subject)	 x	 x	 x x
<u>Safety</u> Adverse events Signs and symptoms of irritation /inflammation (Investigator) Overall assessment (Investigator and subject)	 x x	 x x	 x x x
<u>Subject diary</u> 1st part 2nd part	 x	 x	

** Early drop-out visit in case the subject dropped out.*

7.5. Discussion of the Study Design

The 'Randomised Block' design, chosen for this clinical trial, is a standard method to compare the tolerability of test and comparator drugs. Further discussion of the chosen trial design is not necessary.

8. Selection of Trial Population

8.1. Selection of Patients

Male and female patients meeting all of the inclusion criteria listed in 8.3, but none of the exclusion criteria listed in 8.4 were selected. Patients not meeting any of the inclusion criteria or meeting an exclusion criterion were withdrawn from the trial.

8.2. Number of Patients

80 patients (40 per group) should have been randomized into study so that, at a drop-out rate of 12.5 %, n = 35 patients should have been evaluable per group.

8.3. Inclusion Criteria

1. Male patients and female patients who use an effective contraceptive method or are out of child bearing potential
2. Patient is at least 18 years old
3. Patient suffers from open angle glaucoma or from ocular hypertension
4. The medical condition named in 3 has not been treated pharmacologically before or the patient has undergone a 7 day wash out phase.
5. IOP ≥ 22 mmHg and ≤ 30 mmHg
6. Patient has been informed about the clinical trial and signed the informed consent form

8.4. Exclusion Criteria

1. Eye diseases (except for the ones named in inclusion criterion 3) which require treatment
2. IOP > 30 mmHg
3. Ocular irritations (e.g. edema, redness) at screening
4. Ocular inflammation or present effects of previous eye dis-eases which could influence the results of IOP measurements
5. Other glaucoma or ocular hypertension treatment during the trial
6. Eye surgery 3 month or less prior to screening
7. Concomitant therapy with monoamine oxidase (MAO) inhibitors or with antidepressants which affect noradrenergic transmission (e.g. tricyclic antidepressants and mianserin)
8. Severe or unstable and uncontrolled cardiovascular conditions
9. Severe systemic concomitant diseases
10. Liver or kidney diseases
11. Scheduled major surgeries

12. Enrolment in another clinical trial within the last 4 weeks or during enrolment in this trial
13. Known hypersensitivity to the active ingredient or any excipient of the IMPs
14. Women: pregnancy or lactation
15. Previous or current alcohol or drug abuse
16. Mental or emotional instability that might jeopardize the validity of the informed consent or the compliance with the trial procedures
17. Unreliability or lack of cooperation
18. Other reasons why, in the opinion of the investigator, the patients should not participate in the trial

8.5. Replacement for Dropped out Patients

Dropped out patients were, as intended in the trial protocol, not replaced.

8.6. Early Termination of the Trial

The coordinating investigator could pause or terminate the trial after consulting the sponsor's project manager and under consideration of the associated risks and benefits.

The sponsor had the right to terminate the trial in the event of persistent or repeated major protocol violations, because of risk benefit assessments, administrative reasons, or because of other reasons that made a continuation impossible due to ethical or legal reasons.

On 24th November 2016 the sponsor decided to terminate the trial due to an insufficient recruitment of patients.

All parties involved had to find and implement measures in order to protect the patients' wellbeing. The investigator's and sponsor's obligations regarding documentation and record-keeping were not affected by the early termination. The ethics committees were notified about the early termination.

9. Treatments

9.1. Administration and Dosage

Patients instilled one drop of the IMP (comparator drug or test drug) twice daily into the affected eye(s) (in the morning and in the evening) for 21 days, corresponding to 42 applications. To reduce possible systemic absorption, after instillation, the lachrymal sac should be compressed at the medial canthus (punctual occlusion) with a fingertip for one minute. This was performed immediately following the instillation of each drop. Additionally the application, the safety assessment and occurring symptoms of irritation were documented in the subject diary. The administration was not allowed to be neglected more than twice. In case of loss or damage of the medication the investigator could issue a spare container of medication.

The content of a transparent polyethylene single-dose container of the test drug, Brimonidine UD, was intended for immediate use after opening. Any contents remaining after instillation had to be discarded.

Contact lenses had to be removed before instillation of the IMP and should not be reinserted until at least 15 minutes after instillation.

The white low-density polyethylene screw cap flasks, that contained the comparator drug Alphagan®, were intended for repeated use.

9.2. Identity of Investigational Products

Brimonidine UD (Test drug):

Active ingredient:	One ml solution contains 2.0 mg brimonidine tartrate, equivalent to 1.3 mg of brimonidine.
Excipients:	Citric acid monohydrate
	Hydrochloric acid or sodium hydroxide (for pH-adjustment)
	Poly(vinyl alcohol)
	Sodium chloride
	Sodium citrate
	Water for injections
Dosage form:	Solution in single-dose containers (50 units)

Alphagan® (Comparator drug):

Active Ingredient:	One ml solution contains 2.0 mg brimonidine tartrate, equivalent to 1.3 mg of brimonidine.
Excipients:	0.005 % (w/v) benzalkonium chloride
	Citric acid monohydrate
	Hydrochloric acid or sodium hydroxide (for pH-adjustment)
	Poly(vinyl alcohol)
	Purified water
	Sodium chloride
	Sodium citrate
	Water for injections
Dosage form:	Solution in a flask

9.3. Supply with the IMP, Dispensation, Storage and Return

The sponsor, Pharma Stulln GmbH, supplied the investigators with the IMP and the provisional IMP via the monitors of the SAM® GmbH.

The sponsor packaged and sealed the IMP and the provisional IMP in folding boxes of equal size and weight to assure the blinding of the investigators, study-nurses, monitors and biometricians.

The investigators confirmed the proper reception of the sealed IMP and provisional IMP via the monitors in writing and documented everything in the RDE system. They ensured a safe handling suitable storage conditions (lockable cabinet, storage not above 25 °C).

The investigators were instructed to remind the patients to treat the IMP with appropriate care and to not forward it to third parties. Additionally the investigators were assigned to assure that the patients would only reveal the identity of the given medication at the last visit (completion) or in case of an emergency. Upon the loss or damage of IMP the provisional IMP should be handed to the patients. The procedure should be documented in the RDE system.

The investigators received closed and sealed envelopes, emergency envelopes that contained the applied IMP for the individual patients.

The patients were instructed to return all the used and unused single-dose containers or flasks to the investigator immediately after the completion of their study treatment.

The dispensation and return of the medication was documented in the RDE system.

9.4. Randomization

A randomization plan was generated using the PROC PLAN procedure in SAS, version 9.3. Patients were randomized in a suitable block size and equally distributed to treat-

ment groups. The RDE system assigned individual patient identification numbers to the patients based on the randomization plan.

9.5. Blinding

The patient, the investigator, the monitor and the biometrician were blinded to the identity of the investigational medicinal products (IMPs).

Brimonidine UD was supplied in unit dose vials and Alphagan® in bottles. Both medications were delivered in boxes of identical design and weight, labelled with individual patient identification numbers. The boxes were sealed, thus the identity of the IMP could only be revealed by breaking the seal. The investigator and his staff were not to break the seal. During visit 1, the patient received the IMP box labelled with his individual patient identification number. The patient opened the box with the IMP after leaving the trial site. The patient was not to disclose the identity of the IMP to the investigator or study nurse. The investigator measuring the intraocular pressure (IOP) was therefore masked to the randomization result of the patient. Returned IMP was handed out to the study nurses. After the IOP measurement at visit 3 had been performed by the investigator the drug accountability file of the patient was visible to the study nurse. The study nurse then opened the returned box and counted either the number of the returned vials or weighed the returned bottle and entered the number of returned vials or the weight of the bottle into the remote data entry (RDE) system.

The investigator was provided with a closed and sealed emergency envelope for each patient. The emergency envelope contained the randomization result. Due to the design of the emergency envelope, this information could only be obtained by opening the emergency envelope. The investigator only opened the emergency envelope when it was imperative for the treatment of the patient. When an emergency envelope was opened, the date and reason had to be written on the envelope. This statement had to be signed by the investigator. The sponsor's project manager was to be notified. All emergency envelopes had to be returned to the sponsor after the end of the trial.

9.6. Labelling and packaging

Brimonidine UD and Alphagan® were supplied by the sponsor. Brimonidine UD is bottled in transparent polyethylene single-dose containers. 2 Strips of 5 single-dose containers are packed in an aluminum laminated foil pouch. In total 5 aluminum laminated foil pouch were packed in a sealed folding box. Alphagan® is supplied in white low-density polyethylene bottles. The cap was either a conventional polystyrene cap or a compliance-cap (C-cap).

Both IMPs were delivered in boxes labelled with individual subject identification numbers. The subject identification numbers could be used for unblinding. The boxes had an identical design and weight, regardless of the contents. The boxes were also filled with packing material, in order to prevent the content from being identified by shaking the box. Unit dose vials, pouches and boxes were labelled with the information required by EudraLex Volume 4 Annex 13. For a detailed description and an example of the label see appendix 0.

9.7. Prior and Concomitant Therapy

If a subject was in medical treatment, the primary care physician was contacted prior to randomization, in order to clarify whether an exclusion criterion was applicable. Con-

comitant therapies were possible if no exclusion criterion was met and no effect on the efficacy and safety of the IMP were to be expected. Concomitant medications were documented in the RDE-System (substance, dosage, application and indication).

Any glaucoma or ocular hypertension therapy other than the IMP was not allowed during the trial and resulted in immediate withdrawal of the patient. With amendment 2 participation in the trial was allowed after a 7 days wash out phase of previous glaucoma or ocular hypertension medication.

Brimonidine is contraindicated in patients receiving monoamine oxidase (MAO) inhibitor therapy and patients on antidepressants which affect noradrenergic transmission (e.g. tricyclic antidepressants and mianserin).

Although specific studies on drug interactions have not been conducted with brimonidine, the possibility of an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives or anaesthetics) should be considered.

On the level of circulating catecholamines after administration of eye drops containing brimonidine was no data available. Caution is advised when patients are treated with medications which can affect the metabolism and uptake of circulating amines e.g. chlorpromazine, methylphenidate, reserpine.

After the application of brimonidine containing eye drops, clinically insignificant decreases in blood pressure were noted in some patients. Caution is advised when using medicinal products such as antihypertensives and / or cardiac glycosides concomitantly with brimonidine.

Caution is also advised when initiating (or changing the dose of) a concomitant systemic agent (irrespective of the pharmaceutical form) which may interact with α-adrenergic agonists or interfere with their activity, i.e. agonists or antagonists of the adrenergic receptor (e.g. isoprenaline, prazosin).

9.8. Compliance Control

The compliance of the patients was evaluated on the basis of the subject diary entries. The investigator documented whether IMP primary containers were opened or unopened when they were returned.

To assess the consumption of the test drug Brimonidine UD, the number of used and unused single-dose containers was documented in the RDE system by the investigator. 50 single-dose containers of Brimonidine UD were handed out per patient. During the trial at least 42 single-dose containers (2 containers x 21 days) should be used by each patient.

To assess the consumption of the comparator drug Alphagan®, the returned flask was weighed. The weight was documented in the RDE system by the investigator. The consumption of Alphagan® drops was measured by means of the weight difference. The consumption [g] equals the weight [g] of the flask handed out to the patient at trial start less the weight [g] of the returned flask. 1 drop weighs 0.0315 g (see the investigational medicinal product dossier (IMPD) dated 3rd July 2015, page 9). The full flask (including the screw cap and without the folding box) weighs 10.29 g. The empty flask (including the screw cap and without the folding box) weighs 5.17 g. At least 1.323 g (2 drops x 21 days) of Alphagan® should be used during the trial.

Every application of the medication should additionally be documented in the subject diary by the patients and monitored by the investigators.

10. Efficacy and Safety Variables

10.1. Efficacy Variables

The primary efficacy endpoint was the non-inferiority of Brimonidine UD in the reduction of elevated IOP in the range of 22 to 30 mmHg, as compared to Alphagan®. Thus, the primary variable under consideration was the IOP. For the efficacy analysis, the difference between the IOP at screening and the IOP after 21 days of treatment was assessed.
In addition the overall efficacy assessments by patients and investigators were analysed. See chapter 7.4 for the Schedule of Assessments.

10.2. Safety Variables

The secondary endpoint was the superiority of Brimonidine UD over Alphagan® in regard to the adverse drug reactions. Signs and symptoms of undesirable effects and adverse events were analysed as variables for the safety evaluation of Brimonidine UD. The following signs and symptoms of undesirable effects are parameters for the safety evaluation and can have one of four values (none, little, moderate, severe):

Conjunctival redness

Eyelid redness

Eyelid edema

Burning/stinging of eyes

Pruritus of eyes

Foreign body sensation in eyes

Blurred vision

In addition the overall tolerability assessments by patients and investigators were also analysed. See chapter 7.4 for a Schedule of Assessments.

11. Data Quality Assurance

Before the start of this trial the trial sites were checked for the personnel, technical and organisational requirements for the GCP / ICH compliant conduct of the trial.

The data collected during the trial was entered directly into the electronic case report form (eCRF) by investigators and study nurses, using the remote data entry system (RDE system) ars®. For that cause the investigators were provided with an eCRF based on the CRF. With no prior written or electronic record existing, the data directly entered into the eCRF is defined as source data. The Investigator had to ensure the accuracy, completeness, legibility and timeliness of the data reported in the eCRF as well as the consistency with source documents that were not generated in the eCRF. Data management rules are defined in the data management plan (DMP). Checks and cross checks as well as minimal and maximal values are displayed for each variable. These rules were built into the RDE system to avoid mistakes made by the Investigator during the data entry. Upon implausible entries a corresponding error message was automatically displayed to the investigator, so that the error could be corrected. Missing values were displayed to the investigators in a 'missing value list'. The data managers and monitors of the SAM® GmbH had permanent access to all data entered into the RDE system. They performed data checks to detect implausible or inconsistent entries, checked the entries for completeness.

According to the ICH E6 (R1) GCP guideline, item 8.3.13, and to the EMA/INS/GCP/454280/201033 reflection paper on expectations for electronic data collection tools in clinical trials, requirement 10, the investigator had to print a certified copy of the data captured in the eCRF. The copy had to be stored in the patient health record and to be retained at the investigational site as part of the investigator site file (ICF).

To classify medications (prior and concomitant) by therapeutic class, the WHO drug dictionary (release on 1st March 2015) was used. For the coding of prior and concomitant diseases as well as adverse events, the MedDRA dictionary (version 18.0) was used.

Monitoring

The remote monitoring was conducted daily with the aid of the online RDE system ars®.

In the context of initiating visits of the trial sites the investigators were informed orally and in writing about the details of the trial (ICF, trial protocol, CRF, schedule, patient information leaflet, informed consent of the patients, terms of insurance, literature etc.). The monitors instructed the investigational site personnel regarding the online RDE system ars® and ensured, that all the documents and materials required for the proper conduct of the trial were present at the trial sites.

On 15th December 2016 a close out visit was conducted at the trial site of Dr. Ameye in Dusseldorf with 5 patients. Source data verification was performed.

12. Statistical Methods planned in the Protocol and Determination of Sample Size

12.1. Clinically relevant difference and non-inferiority margin

Primary variable under consideration was the IOP reduction in the course of a three weeks lasting therapy. A difference between two IOP reductions is defined clinically relevant if this difference is ≥ 2 mm Hg. The non-inferiority margin between the standard and the test treatment is chosen as delta = 1.9 mm Hg. Therefore the efficacy of the test treatment is proofed non inferior or better if the right sided 95% confidence region for the expected value of the mean IOP reduction of the standard treatment minus the mean IOP reduction under test treatment is smaller than 1.9 mm Hg.

12.2. Statistical Model

Let the IOP distributions of the two therapy groups “standard therapy” and “test therapy” be realisations of normal distributed random variables X(standard, start), X(standard, end), X(test, start) and X(test, end) at the start and at the end of the study, than the differences D(standard) = X(standard, start) – X(standard, end) and D(test) = X(test, start) – X(test, end) of these variables are normally distributed as well.

Let $\mu_{standard} = E(D_{standard})$ and $\mu_{test} = E(D_{test})$ be the corresponding expected values of these differences with equal variances $\sigma_{standard}^2 = \sigma_{test}^2$. To analyse the non-inferiority of the efficacy of the test therapy compared to the efficacy of the standard therapy, the hypothesis

H_{01}: $\mu_{standard} - \mu_{test} \geq 1.9$ mmHg

was tested against

H_{11}: $\mu_{standard} - \mu_{test} < 1.9$ mmHg

by using a one-sided *t*-test for independent samples with a type I error rate of α = 0,05 and a type II error rate of ß = 0,05, for a clinically relevant difference d = 2 mmHg with a standard deviation of s = 2.5 mmHg, estimated from former trials.

12.3. Determination of Sample Size

For the above mentioned decision criteria (see Cohen, 1977) n = 35 patients were necessary per group for the analysis. Assuming a drop-out rate of 12.5 %, 40 patients had to be randomized into each of the therapy groups.

12.4. Definition of planned Analysis Sets

Validity for the per protocol analysis set (PP-set)

All patients whose data on the primary efficacy variable has been documented completely and for whom no protocol violation occurred were included into the per protocol analysis set.

Validity for the per intention to treat analysis set (ITT-set)

Patients whose data on the primary variable has been documented at the start of therapy and at the end of therapy, were included into the intention to treat analysis set.

Validity for the safety analysis set (SA-set)

Any patient applying the IMP during the course of the trial was included into the safety analysis set (= analysis of “drug related events”, and of “all events” for patients not included into the trial but applying the IMP).

12.5. Applied Software

For the data entry, the data management and the data analysis, the validated analysis software SAS version 9.3 for Windows was applied.

13. Changes in the Conduct of the Study and planned Analysis

13.1. Protocol Amendments

Amendment 1

On 6th November 2015, the protocol amendment version 1.0 was submitted to the BfArM and on 23rd November 2015 to the ethics committee. The amendment was concerning the labelling of the IMP. On 24th November 2015, amendment 1 was approved by the BfArM and on 14th December 2015 by the ethics committee.

Amendment 2

On 28th June 2016, the protocol amendment version 2.0 was submitted to the ethics committee and the federal authority. Content of the amendment was the changing of the inclusion criterion 4 by the addition of a 7 days lasting wash out phase. Prior to the amendment only untreated glaucoma or ocular hypertension patients were accepted. The amendment was resolved in consultation with Prof. Lohmann and Dr. Reznicek of the technical university in Munich to improve the recruitment of patients. Amendment 2.0 was approved on 11th July 2016 by the BfArM and on 20th July 2016 by the mainly responsible ethics committee.

Amendment 3

On 9th November 2016, the sponsor, Pharma Stulln GmbH, decided to terminate the trial prematurely due to an insufficient recruitment rate of patients. There were no safety reasons for the termination of the trial and after the termination none of the patients was further treated with the test drug. This was communicated to the BfArM and the ethics committee on 24th November 2016 by telephone and in writing on 29th November 2016. The BfArM confirmed the termination of the trial on 5th December 2016.

13.2. Change of Analysis Sets

Because of the small number of patients there was no assignment into the planned analyses sets ITT, PP or SA (see 12.4 Definition of planned Analysis Sets). Patients were differentiated according to their treatment Groups (Brimonidine UD or Alphagan®).

14. Study Patients

14.1. Patient Collective

From 9th March 2016 until 31st October 2016, 8 patients were screened and randomised at 3 out of 6 initiated trial sites, 7 of which completed the trial regularly and 1 of which terminated the trial prematurely (0.).

Number of Patients Randomized as well as Number of Patients that Completed the Trial regularly and Dropped Out, respectively (differentiated according to Trial Sites and Treatment Groups)

		Drop-out		Completed study		Total	
		N	%	N	%	N	%
1: Dr. Mende	Brimonidine UD	0	0	0	0	0	0
	Alphagan®	0	0	0	0	0	0
2: Dr. Ameye	Brimonidine UD	0	0.0	3	100.0	3	100.0
	Alphagan®	1	50.0	1	50.0	2	100.0
3: Prof. Dr. Lohmann	Brimonidine UD	0	0	0	0	0	0
	Alphagan®	0	0.0	1	100.0	1	100.0
4: Dr. Neuhann	Brimonidine UD	0	0.0	1	100.0	1	100.0
	Alphagan®	0	0.0	1	100.0	1	100.0
5: Dr. Klamann	Brimonidine UD	0	0	0	0	0	0
	Alphagan®	0	0	0	0	0	0
6: PD Dr. Dr. Lorenz	Brimonidine UD	0	0	0	0	0	0
	Alphagan®	0	0	0	0	0	0
Total		1	12.5	7	87.5	8	100.0

N = Number of patients

4 patients were treated with the test drug Brimonidin UD and 4 patients were treated with the comparator drug Alphagan®. One patient, treated with Alphagan®, terminated the trial early due to the adverse drug reaction “allergic reaction at the application point” (Listing 14.1.1).

Number of Patients Randomized as well as Number of Patients that Completed the Trial regularly and Dropped Out, respectively (differentiated according to Treatment Groups)

	Drop-out		Completed study		Total	
	N	%	N	%	N	%
Brimonidine UD	0	0	4	100.0	4	100.0
Alphagan®	1	25.0	3	75.0	4	100.0
Total	1	12.5	7	87.5	8	100.0

N = Number of patients

Listing 14.1.1 Patients that Dropped Out of the Trial

Treatment	Pat. No	Age (years)	Gender	Duration of the application (days)	Reason for dropout
Alphagan®	5	81	Male	4	Application site allergy

14.2. Demographic Data

In the Brimonidine UD group women were treated exclusively. In the Alphagan® group half of the participants was male (0).

Gender Distribution

	Male		Female		Total	
	N	%	N	%	N	%
Brimonidine UD	0	0	4	100.0	4	100.0
Alphagan®	2	50.0	2	50.0	4	100.0
Total	2	25.0	6	75.0	8	100.0

N = Number of patients

The average age of the patients was 70.6 years (all Caucasian). The youngest patient was 53 years and the eldest patient 81 years old (0).

Age Distribution within the Trial

	N	Missing	Mean	Std. dev.	Minimum	Maximum	Median
Brimonidine UD	4	0.0	73.5	5.6	66.0	79.0	74.5
Alphagan®	4	0.0	67.8	13.0	53.0	81.0	68.5
Male	2	0.0	67.0	19.8	53.0	81.0	67.0
Female	6	0.0	71.8	6.9	61.0	79.0	74.5
One eye	0	0.0	0.0	0.0	0.0	0.0	0.0
Both eyes	8	0.0	70.6	9.8	53.0	81.0	74.5
Total	8	0.0	70.6	9.8	53.0	81.0	74.5

N = Number of patients

Detailed information by patient are in the following Listing 14.2.1.:

Listing 14.2.1. Demographic Data: Age, Gender, Height, Ethnicity

Pat. No	Age (years)	Gender	Height [cm]	Ethnicity
5	81	Male	174	Caucasian
6	66	Female	165	Caucasian
7	79	Female	164	Caucasian
8	61	Female	159	Caucasian
9	73	Female	161	Caucasian
17	76	Female	161	Caucasian
25	53	Male	180	Caucasian
26	76	Female	160	Caucasian

14.3. Medical History

In all 8 patients an elevated IOP between 22 and 30 mmHg was measured.

In the Brimonidine UD group each patient was diagnosed with an open angle glaucoma, whilst in the comparator drug group 1 patient was diagnosed with ocular hypertension (0).

Number of Eyes Affected with Open Angle Glaucoma or Ocular Hypertension

	Open angle glaucoma		Ocular hypertension		Total	
	N	%	N	%	N	%
Brimonidine UD	8	100.0	0	0.0	8	100.0
Alphagan®	6	75.0	2	25.0	8	100.0
Total	14	87.5	2	12.5	16	100.0

N = Number of eyes affected

Regarding previous diseases, in 1 patient from the Alphagan® group the previous disease “precancerous skin lesion, face” was documented.

Concerning concomitant diseases, for 1 patient from the Brimonidine UD group an elevated blood pressure reading without diagnosis of hypertension was documented.

As concomitant medication, 1 patient applied Evotears drops during the trial against dry eyes.

For more details of all affected patients regarding their medical history see the data listings compilation in appendix 20.2 (Listing 3.1 – 3.6).

14.4. Measurement of Treatments

In total the IMP was applied 590 times during the course of the trial. Brimonidine UD was applied 312 times and Alphagan® was applied 278 times (0).

Number of Applications of the IMP

	N	Missing	Mean	Std. dev.	Median	Min	Max	Total number of applications
Brimonidine UD	8	0	78	12.0	84	60	84	312
Alphagan®	8	0	70	38.6	86	12	94	278
Total	16	0	74	26.8	84	12	94	590

N = Number of eyes affected
84 Applications per patient throughout the 21 days of treatment

An overview of all patients and which treatment they received is displayed in the following Listing 14.4.1.:

Listing 14.4.1. Patients Differentiated according to their Trial Site

Site	Pat. No	Treatment
2: Dr. Ameye, Düsseldorf	5	Alphagan®
	6	Brimonidine UD
	7	Brimonidine UD
	8	Alphagan®
	9	Brimonidine UD
3: Prof. Dr. Lohmann, Munich	17	Alphagan®
4: Dr. Neuhann, Munich	25	Alphagan®
	26	Brimonidine UD

14.5. Protocol Deviations

There occurred no protocol deviations in this study.

15. Efficacy Evaluation

15.1. Efficacy Results

Before the start of treatment, the mean IOP measured in the Brimonidine UD group was 24 mmHg and the mean IOP measured in the Alphagan® group was 25 mmHg. These values decreased on average to 16 mmHg (Brimonidine UD) and 18 mmHg (Alphagan®) at the end of treatment (Visit 3) (0).

Distribution of the Intraocular Pressure [mmHg] during the Trial

		N	Missing	Mean	Std. dev.	Median	Q25	Q75	Min	Max
IOP at visit 1	Brimonidine UD	8	0	24	1.9	24	23	25	22	28
	Alphagan®	8	0	25	2.8	24	23	27	22	29
IOP at visit 2	Brimonidine UD	8	0	19	1.9	18	18	19	17	23
	Alphagan®	6	2	23	2.3	23	21	26	21	26
IOP at visit 3	Brimonidine UD	8	0	16	1.1	17	16	17	14	17
	Alphagan®	6	2	18	1.0	18	18	18	16	19

N = Number of eyes affected
IOP = Intraocular pressure

The mean IOP decrease between Visit 1 and Visit 2 was 5.63 mmHg after treatment with Brimonidine UD and 1.67 mmHg after treatment with Alphagan® (0).

The mean IOP decrease between Visit 1 and Visit 3 was 7.88 mmHg after treatment with Brimonidine UD and 7.17 mmHg after treatment with Alphagan® (0).

Distribution of the Change of the Intraocular Pressure [mmHg] in both Treatment Groups between Visit 1 and Visit 2

	N	Missing	Mean	Std. dev.	Median	Q25	Q75	Min	Max	P value
Brimonidine UD	8	0	5.63	1.60	5.00	5	6	4	9	<.0001
Alphagan®	6	2	1.67	1.21	1.50	1	3	0	3	0.0199

N = Number of eyes affected
Intraocular pressure (IOP) at visit 1 minus IOP at visit 2 [mmHg]

P value: t test, alpha = 0.05

Distribution of the Change of the Intraocular Pressure [mmHg] in both Treatment Groups between Visit 1 and Visit 3

	N	Missing	Mean	Std. dev.	Median	Q25	Q75	Min	Max	P value
Brimonidine UD	8	0	7.88	2.36	7.00	7	9	5	12	<.0001
Alphagan®	6	2	7.17	2.79	6.50	5	10	4	11	0.0015

N = Number of eyes affected
Intraocular pressure (IOP) at visit 1 minus IOP at visit 3 [mmHg]

P value: t test, alpha = 0.05

A detailed Listing of all measurements of IOP by patient in this trial is listed in Listing 4.1 in appendix 20.2.

15.2. Overall Efficacy Assessments of the IMP by Investigators and Patients

In total, the efficacy of Brimonidine UD was evaluated with 'very good' by the investigators in 100 % of the cases and by the patients in 75 % of the cases (0 and 0).

Overall Efficacy Assessment of the IMP by the Investigators after 21 days

	Very good		Good		Moderate		None		Missing		Total	
	N	%	N	%	N	%	N	%	N	%	N	%
Brimonidine UD	4	100.0	0	0.0	0	0.0	0	0.0	0	0.0	4	100.0
Alphagan®	2	50.0	1	25.0	0	0.0	0	0.0	1	25.0	4	100.0

N = Number of patients

Overall Efficacy Assessment of the IMP by the Patients after 21 days

	Very good		Good		Moderate		None		Missing		Total	
	N	%	N	%	N	%	N	%	N	%	N	%
Brimonidine UD	3	75.0	1	25.0	0	0.0	0	0.0	0	0.0	4	100.0
Alphagan®	1	25.0	2	50.0	0	0.0	0	0.0	1	25.0	4	100.0

N = Number of patients

15.3. Efficacy Conclusion

A valid evaluation of efficacy of Brimonidine UD versus Alphagan® cannot be made due to the small number of patients.

16. Safety Evaluation

16.1. Adverse Events (AE)

Overall 3 adverse events with causal relation to the IMP (adverse drug reaction, ADR) were reported affecting 2 patients. The ADR 'allergic reaction at the application point' with certain causality in the Alphagan® group led to the premature termination of the treatment by the affected patient no. 5 (0). For Patient no. 26 the ADR blurred vision and eyes stinging with the causality possible and likely were documented.

During the trial no Death, serious adverse event (SAE) or serious adverse drug reaction (SADR) occurred.

Nature of the Adverse Drug Reactions (ADR)

				Brimonidine UD		Alphagan®		Total	
				N	%	N	%	N	%
Pat. No	ADR	Causality	Intensity						
5	Application site allergy	Certain	Severe	0	0	1	100.0	1	100.0
26	Blurred vision	Possible	Severe	1	100.0	0	0	1	100.0
	Eyes stinging	Likely	Severe	1	100.0	0	0	1	100.0
Total				2	66.7	1	33.3	3	100.0

N = Number of adverse drug reactions (ADR)

16.2. Undesirable Effects

The evaluation of the subject diary entries concerning the occurrence of signs and symptoms of undesirable effects led to the following result (0 and Listing 16.2.1).

In total, throughout the 590 applications, 32 (5.4 %) symptoms of undesirable effects were documented.

According to the subject diaries, Brimonidine UD was applied 312 times and Alphagan® 266 times. In the Brimonidine UD group 3 patients together showed 25 events of symptoms of undesirable effects (4.2 % of the total number of applications of the test and the comparator drug). 21 of these symptoms were documented by 1 patient (No 26).

In the Alphagan® group, 2 patients together documented 7 events of symptoms of undesirable effects (1.2 % of the total number of applications of the test and the comparator drug). In 1 additional patient of this group an allergic reaction at the application point led to a premature termination of the trial participation.

The symptom ‘Blurred vision’ occurred 10 times with varying intensity (5 times minor, 2 times moderate, 3 times severe) in 2 patients applying Brimonidine UD (3.2 % of the applications of Brimonidine UD) and 4 times with minor intensity in a patient applying Alphagan® (1.5 % of the applications of Alphagan®).

The symptom ‘Burning/stinging of the eye’ occurred 4 times in total in 2 patients applying Brimonidine UD (1.3 % of the applications of Brimonidine UD). The intensity of the symptom was evaluated as minor 2 times and as severe also 2 times.

The symptom ‘Foreign body sensation in the eye’ occurred once with minor intensity in a patient applying Brimonidine UD (0.3 % of the applications of Brimonidine UD) and 2 times with minor intensity in a patient applying Alphagan® (0.8 % of the applications of Alphagan®).

The symptom ‘Pruritus of the eye’ occurred once with minor intensity in a patient applying Brimonidine UD (0.3 % of the applications of Brimonidine UD) and once with minor intensity in a patient applying Alphagan® (0.4 % of the applications of Alphagan®).

The symptom ‘Eyelid edema’ was documented 3 times by a patient applying Brimonidine UD (1.0 % of the applications of Brimonidine UD) The intensity of the symptom was evaluated 2 times as moderate and once as severe.

The symptom ‘Conjunctival redness’ occurred 4 times in a patient applying Brimonidine UD (1.3 % of the applications of Brimonidine UD) 3 of which with minor intensity and once with moderate intensity.

The symptom ‘Eyelid redness’ occurred 2 times in a patient applying Brimonidine UD (0.6 % of the applications of Brimonidine UD) with minor intensity.

Number of Symptoms of Undesirable Effects during the 21 days of Treatment

Symptoms of undesirable effects	Brimonidine UD	Alphagan®
	N	N
Blurred vision	10	4
Burning/stinging of the eye	4	0
Foreign body sensation in the eye	1	2
Pruritus of the eye	1	1
Eyelid edema	3	0
Conjunctival redness	4	0
Eyelid redness	2	0
Total	25	7

N = Number of symptoms of undesirable effects

Listing 16.2.1. Patients that showed Symptoms of Undesirable Effects during the 21 days of Application of the IMP

Study medication	Pat. No	Symptom	Day of application	Affected eye	Intensity
Alphagan®	8	Foreign body sensation in the eye	1	Left	Minor
		Foreign body sensation in the eye	12	Left	Minor
		Pruritus of the eye	12	Left	Minor
	25	Blurred vision	1	Left	Minor
		Blurred vision	1	Left	Minor
		Blurred vision	1	Right	Minor
		Blurred vision	1	Right	Minor
Brimonidine UD	6	Blurred vision	1	Left	Minor
		Blurred vision	1	Right	Minor
		Blurred vision	2	Left	Minor
	7	Burning/stinging of the eye	1	Right	Minor
	26	Blurred vision	2	Right	Minor
		Blurred vision	4	Left	Minor
		Blurred vision	4	Right	Severe
		Blurred vision	8	Right	Severe
		Blurred vision	8	Right	Severe
		Blurred vision	10	Right	Moderate
		Blurred vision	13	Right	Moderate
		Burning/stinging of the eye	3	Right	Severe
		Burning/stinging of the eye	3	Right	Severe
		Burning/stinging of the eye	7	Right	Minor
		Conjunctival redness	2	Right	Missing
		Conjunctival redness	4	Left	Moderate
		Conjunctival redness	5	Left	Minor
		Conjunctival redness	5	Right	Minor
		Conjunctival redness	13	Right	Minor
		Eyelid edema	4	Right	Moderate
		Eyelid edema	11	Left	Severe
		Eyelid edema	14	Right	Moderate
		Eyelid edema	14	Right	Missing
		Eyelid redness	1	Left	Missing
		Eyelid redness	10	Right	Minor
		Eyelid redness	10	Right	Minor
		Foreign body sensation in the eye	9	Right	Minor
		Pruritus of the eye	5	Right	Minor

Intensity = Missing: No documentation on the occurrence of the symptom

16.3. Overall Tolerability Assessment of the IMP by the Investigators and patients

The tolerability of Brimonidine UD was evaluated with 'very good' by the investigators in 100 % of the cases (0) and by the patients in 75 % of the cases. One patient evaluated the tolerability with 'good' (0).

The tolerability of Alphagan® was evaluated with 'very good' in 50 % of the cases and with 'good' in 25 % of the cases by both, investigators and patients. An evaluation by the drop out patient (allergic reaction at the application point) applying Alphagan® is missing.

Overall Tolerability Assessment of the IMP by the Investigators after 21 days

	Very good		Good		Moderate		Bad		Missing		Total	
	N	%	N	%	N	%	N	%	N	%	N	%
Brimonidine UD	4	100.0	0	0.0	0	0.0	0	0.0	0	0.0	4	100.0
Alphagan®	2	50.0	1	25.0	0	0.0	0	0.0	1	25.0	4	100.0

N = Number of patients

Overall Tolerability Assessment of the IMP by the Patients after 21 days

	Very good		Good		Moderate		Bad		Missing		Total	
	N	%	N	%	N	%	N	%	N	%	N	%
Brimonidine UD	3	75.0	1	25.0	0	0.0	0	0.0	0	0.0	4	100.0
Alphagan®	2	50.0	1	25.0	0	0.0	0	0.0	1	25.0	4	100.0

N = Number of patients

16.4. Safety Conclusion

For a valid analysis at least 35 patients per treatment group (Brimonidine UD or Alphagan® would have had to participate in and complete the trial regularly. Due to the insufficient number of patients an evaluation is not possible.

17. Discussion and Overall Conclusion

Objective of the clinical trial was to demonstrate the efficacy and safety of the preservative-free formulation Brimonidine UD in the reduction of elevated intraocular pressure (IOP). The primary efficacy endpoint was the non-inferiority of Brimonidine UD in the reduction of elevated IOP in the range of 22 – 30 mmHg as compared to the preserved formulation Alphagan®.

The secondary endpoint was to prove the superiority of Brimonidine UD vs. Alphagan® regarding side effects. Symptoms of ocular irritation and adverse events (AE) were analysed as safety parameters.

For a valid analysis based on the above mentioned decision criteria n = 35 patients should have been included in each validation group. Assuming a drop-out rate of 12.5 %, each therapy group would have had to consist of n = 40 patients. In total n = 80 patients would have had to be randomized into the trial.

The prospective, controlled, randomized, investigator-masked, multicenter, phase III trial was conducted between 9th March 2016 and 31st October 2016 at 6 trial sites.

Male patients and non-pregnant female patients, who used an effective contraceptive method or were out of child bearing potential, older than 18 years and suffering from open angle glaucoma or ocular hypertension with an IOP ≥ 22 mmHg and ≤ 30 mmHg were included into the trial. Before 20th July 2016 only untreated patients, more precisely patients that had not received any treatment of the glaucoma or ocular hypertension until the date of screening, were included. After 20th July 2016, previously treated patients that had undergone a 7 days wash out phase could also be included, according to the protocol amendment 2.0.

After the patient consultation and the informed consent of the patients, the screening started. During the initial examination, the IOP was measured, signs and symptoms of ocular irritation and the inclusion and exclusion criteria were assessed. After the successful inclusion, the patient was randomized electronically into the Brimonidine UD or the Alphagan® group. The investigational medicinal product (IMP) was handed out to the patient with the investigator remaining blinded. The patients were instructed to drip the IMP into the affected eyes for a period of 21 days. Additionally they documented every application of the IMP and the occurrence of the symptoms conjunctival redness, eyelid redness, eyelid edema, burning / stinging of the eye, pruritus of the eye, foreign body sensation in the eye and blurred vision in a paper subject diary. On day 14 and on day 21 after the screening the investigator examined the eyes, measured the IOP again, reviewed the subject diary and documented the occurrence of AE or symptoms of ocular irritation. Treatment of the elevated IOP other than the IMP was not permitted. On the final examination (day 21) the investigator assessed the patients' compliance by regarding the consumption of the returned IMP. In addition, the investigator and the patient evaluated the efficacy and safety of the IMP. The patients were able to terminate their participation in the trial prematurely at any time, without giving reasons.

At 3 out of 6 trial sites 8 patients were recruited between 9th March 2016 and 30th October 2016. 7 patients thereof completed the trial regularly. 1 patient applying Alphagan® terminated the trial participation prematurely because of the occurrence of the adverse drug reaction (ADR) 'allergic reaction at the application point'.

The subsequent implementation of a 7 days wash out phase for the inclusion of previously already treated glaucoma patients (protocol amendment 2.0 dated 20th July 2016) did not improve the patient recruitment rate. Therefore the sponsor, Pharma Stulln GmbH, decided to terminate the trial prematurely due to insufficient patient recruitment in November 2016.

6 (75 %) of the participants were female and 2 (25 %) were male. The male patients both applied Alphagan®. The average age was 70.6 years.

The application of Brimonidine UD led to an average IOP decrease of 7.88 mmHg and the application of Alphagan® effected an average IOP decrease of 7.17 mmHg.

Altogether, 3 ADR occurred in 2 patients. 2 out of these 3 ADR occurred in the Brimonidine UD treatment group. Serious adverse events (SAE) or serious adverse drug reactions (SADR) did not occur during the trial.

In total, throughout 590 applications, 32 symptoms of ocular irritation were documented in the subject diaries. 25 thereof occurred during the 312 applications of Brimonidine UD. During the 266 applications of Alphagan® 7 symptoms of ocular irritation were reported. 21 (67.2 %) of the reported symptoms of ocular irritation were documented by one patient (No 26) treated with Brimonidine UD. This patient was concomitantly treated with Evotears drops against dry eyes.

The tolerability of Brimonidine UD was evaluated with ‘very good’ by the investigators in 100 % of the cases and by the patients in 75 % of the cases. One patient evaluated the tolerability with ‘good’.

A valid evaluation of the tolerability and safety of Brimonidine UD cannot be made due to the small number of patients.

18. Tables and Listings

For a complete compilation of all tables and listings in this study see “List of tables” and “Listings” in appendix 20.2.

Overview of tables and listings

	Study report	List of tables	Listings
General course of the study	Chapter 14.1.	Table 1.1 - 1.12	Listing 1.1 - 1.3
Demographic data	Chapter 14.2.	Table 2.1 - 2.5	Listing 2.1
Medical history	Chapter 14.3.	Table 3.1 - 3.14	Listing 3.1 - 3.6
Measurement of treatments	Chapter 14.4.	Table 1.7	
Efficacy	Chapter 15.1. - 15.2.	Table 4.1 - 4.4	Listing 4.1 – 4.2
Safety	Chapter 16.1. - 16.3.	Table 5.1 - 5.32	Listing 5.1 – 5.6

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20. Appendices

20.1. Study Information

Protocol and Protocol Amendments

List of IEC, patient information and informed consent form

List and CVs of Investigators

Study medication

20.2. Patient Data Listings

Listings

List of Tables

20.3. Case Report Form

Case Report Form

Subject Diary

21. Signatures

Author:

_____ _____

Dr. Dieter Werdier — Date

CEO, Biostatistician

SAM® GmbH
Am Gut Wolf 3
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Germany

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Sponsor's responsible person:

_____ _____

Dr. Karl Luschmann — Date

CEO, Qualified Person

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