AZAD Pharma AG

CLINICAL STUDY REPORT

A PHASE III, MULTICENTRE, RANDOMISED, INVESTIGATOR-MASKED, CROSS- OVER, COMPARATIVE CLINICAL TRIAL EVALUATING THE EFFICACY AND SAFETY OF THE GENERIC BRINZOLAMIDE 10 MG/ML + TIMOLOL 5 MG/ML EYE DROPS SUSPENSION (AZAD PHARMA AG) WITH BRINZOLAMIDE 10 MG/ML + TIMOLOL 5 MG/ML EYE DROPS SUSPENSION AZARGA® (ALCON LTD) IN OPEN-ANGLE GLAUCOMA AND OCULAR HYPERTENSION PATIENTS

Product:	Brinzolamide 10 mg/ml + Timolol 5 mg/ml eye drops suspension (AZAD Pharma AG)
Indication studied:	Open angle glaucoma, ocular hypertension
Development Phase of Study:	Phase III, therapeutic equivalence
Short description of study:	Multicentre, randomised, investigator-masked, cross- over, comparative clinical trial to show therapeutic equivalence of Brinzolamide 10 mg/ml + Timolol 5 mg/ml eye drops suspension (AZAD Pharma AG) to Brinzolamide 10 mg/ml + Timolol 5 mg/ml eye drops suspension Azarga® (Alcon Ltd) in patients with open angle glaucoma and ocular hypertension
EudraCT Number:	2016-000946-69
Clinical Trial Identification:	AZ07
Study Initiation Date:	First Patient Screened: 11.08.2016
Date of Early Study Termination:	not applicable
Study Completion:	Last Patient Completed: 18.05.2017
Study Report Version	Version 01, dated 15-AUG-2017
Release Date	22-AUG-2017
Replaces Previous Version:	N/A

This clinical study was performed in compliance with current Good Clinical Practice (GCP) and all essential documents are archived in the Clinical Trial Master File.

SPONSOR INFORMATION AND PRINCIPAL INVESTIGATOR

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A list of authors and signatures are provided in appendices 16.1.3.6 and 16.1.4 of this report.

CONFIDENTIALITY STATEMENT

2 SYNOPSIS

Name of Sponsor/company:	AZAD Pharma AG
Name of Finished Product:	Brinzolamide 10 mg/ml + Timolol 5 mg/ml eye drops suspension (AZAD Pharma AG)
Name of Active Ingredient(s)	Brinzolamide 10 mg/ml + Timolol 5 mg/ml
Title of Clinical Study:	A Phase III, Multicentre, Randomised, Investigator-masked, Cross-over, Comparative Clinical Trial Evaluating the Efficacy and Safety of the Generic Brinzolamide 10 mg/ml + Timolol 5 mg/ml Eye Drops Suspension (AZAD Pharma AG) with Brinzolamide 10 mg/ml + Timolol 5 mg/ml Eye Drops Suspension Azarga® (Alcon Ltd) in Open-Angle Glaucoma and Ocular Hypertension Patients
Investigator(s) and Study Centres	Coordinating Investigator: Prof Dr. med G. Garhöfer, Medical University of Vienna, Austria. Nine (9) study sites (1 in Austria, 3 in Poland, 5 in Hungary) participated.
Main inclusion/exclusion criteria	<u>Main Inclusion Criteria:</u> 1. Elevated IOP / primary open angle glaucoma (irideocorneal angle > 30°) in at least one eye: mean diurnal IOP pre-treatment (measured at approx. 8 am 10 am and 4 pm must be equal or higher than 22 mmHg, and equal or lower to 35 mmHg (untreated, i.e. naïve or after washout). 2. Not on any ophthalmic pressure-lowering medication, or in the condition not to suffer any untoward effects by withdrawal from current pressure-lowering medications for the wash-out period(s). 3. Male or female patients, 18-75 years old. <u>Main Exclusion Criteria:</u> 1. Visual acuity of less than distance Snellen 20/100 (decimal 0.20 or 0.70 logMAR) in either eye. 2. Evidence of acute ocular infection, corneal foreign body, or ocular inflammation. 3. Previous significant ocular trauma, laser or incisional surgery within 3 months of the screening visit. 4. Any corneal abnormalities preventing reliable applanation tonometry. 5. Patients with risk of angle closure or evidence of acute, intermittent, or chronic angle closure. 6. Types of glaucoma other than primary open angle glaucoma (POAG).
Publications and References	Not applicable.
Studied Period:	Date of first screening/enrolment: 11.08.2016 Date of last patient completed: 18.05.2017

Phase of Development	Phase III
Objectives	Primary objective: to evaluate the efficacy of the generic Brinzolamide 10 mg/ml + Timolol 5 mg/ml eye drops suspension AZAD Pharma AG (test product) in lowering intra-ocular pressure (IOP) when compared to Brinzolamide 10 mg/ml + Timolol 5mg/ml eye drops suspension product Azarga®, Alcon Ltd) (reference product). Secondary objectives: • To compare the tolerance of the test and reference products using an ocular comfort level score. • To compare the levels of conjunctival hyperaemia induced by test product and reference product. • To evaluate the general safety of the test product compared to the reference product.
Methodology	The trial was set-up as a phase III, multicentre, randomised, investigator-masked, cross-over comparative clinical trial. Patients already treated with IOP lowering medication had to follow a 28-day wash-out period. Patients were assigned in a 1:1 ratio to receive either test or reference product in treatment period I (21 days), followed by an additional wash-out period (28 days), before starting treatment period II (21 days). Patients who were assigned to receive test product in period I received reference product in period II and vice versa.
Number of Patients	Planned: 66 patients included and 54 patients evaluable (per protocol). Effectively analysed: 66 for safety; 55 per protocol.
Indication	Primary open angle glaucoma, ocular hypertension.
Test Product, Dose and Mode of Administration, Batch Number	Generic Brinzolamide 10 mg/ml + Timolol 5 mg/ml eye drops suspension, AZAD Pharma AG, (investigator-masked). One drop to be instilled into the eye(s) twice daily (morning and evening). Batch Number:16DQ072
Reference Product, Dose and Mode of Administration, Batch Number	Azarga: Brinzolamide 10mg/ml + Timolol 5mg/ml eye drops suspension, Azarga®, Alcon Ltd, (investigator masked). One drop to be instilled into the eye(s) twice daily (morning and evening). Batch Number: 16B08CD
Duration of Treatment	21 days (± 1 day) in Period 1 and 21 days (± 1 day) in period II, total: 42 days.
Criteria for Evaluation of Primary and Secondary Endpoints	Primary Endpoint: The primary endpoint is the difference between the test product and the reference product with respect to the differences in the mean diurnal IOP pre- and post-treatment in the study eye. IOP was determined using a Goldmann Applanation Tonometer. On Day 1 (baseline, before treatment) and on Day 22 (under treatment), mean diurnal IOP (mmHg) of the study eye is calculated as the average of 3 IOP measurements at approximately 8

	am (± 1 hour), 10 am (i.e. 2 hours ± 30 min after first measurement) and 4 pm (i.e. 8 hours ± 30 min after first measurement). The IOP lowering effect corresponded to the difference in the mean diurnal IOP in the study eye between Day 1 and Day 22 (positive value). Secondary Endpoints: Ocular tolerance: The difference between the test and reference products with respect to ocular comfort level score and conjunctival hyperaemia was evaluated at baseline (Day 1) and Day 22 in both periods. Safety: The difference between the test and reference products with respect to general safety as assessed by occurrence of adverse events. The occurrence of AEs was summarized in frequency tables by treatment group, period and overall and was listed in data listings and the differences in frequency of AEs were tested with Fisher's Exact Test.
Statistical Methods	Non-inferiority between the test product and the reference product was tested using a mixed linear model. The effect of treatment was calculated as the difference between the mean diurnal IOP in the study eye after 21±1 days of treatment and at baseline (pre-treatment). The non-inferiority margin was set to 1.5 mmHg for the difference in treatment effect between the test and reference product. The efficacy analysis was performed on the PP population and repeated as sensitivity analysis on the ITT population to assess the robustness of the study results.
Summary and Conclusion	Primary endpoint - Efficacy Results: Test product Brinzolamide 10 mg/ml + Timolol 5 mg/ml eye drops suspension, AZAD Pharma AG is non-inferior to the reference product Azarga®, Alcon Ltd, using a linear mixed model non-inferiority analysis and a non-inferiority level of 1.5 mmHg (PP population n=55). Secondary endpoints – Ocular Tolerance and Safety Results: there were no significant statistical differences between the Test product (AZAD Pharma AG) and the reference product Azarga® with respect to maximal ocular discomfort and conjunctival hyperaemia. The difference in the incidence of adverse events (AE) was not significant for both products. Serious adverse events (SAEs) did not occur for both products. Conclusion: The IOP lowering effect of Test product (AZAD Pharma AG) is non-inferior to the reference product Azarga®. Test product (AZAD Pharma AG) and Azarga® were equally well tolerated and safe as shown by the ocular tolerance level and hyperaemia scores, as well as by the incidence of AE and the absence of SAEs. Any differences in the ocular tolerance and safety parameters were not statistically significant.
Date of report	15 August 2017