Clinical Development
Picotamide in the Prophylaxis of Migraine with Aura
Clinical Study Report

Study No: 19122011

EudraCT No.: 2011-006207-36

A multi centre, double blind, randomised, placebo controlled crossover study to evaluate the efficacy and tolerability of picotamide in the prophylaxis of migraine in patients presenting with migraine with aura

Document type:	Clinical Study Report		
Development phase:	Phase II	**Protocol No.:**	**19122011**
First subject enrolled:	July 11, 2012	**Last subject completed**:	October 12, 2016
Principal investigator:	Prof. Jes Olesen, M.D., Danish Head Center, Department of Neurology, Glostrup Hospital, DK-2600 Glostrup, Denmark		
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Sponsor signatory	Proreo Pharma Innovation AG, Weierweg 7, CH-4410 Liestal, Switzerland		
Document status:	Final Version 1.0	Release date:	June 06, 2018

1. SIGNATURES

Study:
A multi centre, double blind, randomised, placebo controlled crossover study to evaluate the efficacy and tolerability of picotamide in the prophylaxis of migraine in patients presenting with migraine with aura.

Authors:

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

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2. SYNOPSIS

Name of Sponsor/Company: **Proreo Pharma Innovation AG**		
Name of Finished Product: **Plactidil**		
Name of Active Ingredient: **Picotamide**		
Title of Study: **A multi centre, double blind, randomised, placebo controlled crossover study to evaluate the efficacy and tolerability of picotamide in the prophylaxis of migraine in patients presenting with migraine with aura.**		
Investigator: Prof. Jes Olesen, M.D.		
Study centre: Danish Headache Center, Department of Neurology, Glostrup Hospital, DK-2600 Glostrup, Denmark		
Publication (reference): None		
Study period (years): 4 Phase of development: II (date of first enrolment) July 11, 2012 (date of last completed) October 12, 2016		
Objectives: *Primary objective*: • To investigate the efficacy of picotamide compared to placebo in the reduction of the number of auras in patients with migraine with aura. *Secondary objectives*: 1. To compare the safety and tolerability of picotamide and placebo in the prophylactic treatment of patients with migraine with aura; 2. To investigate the efficacy of picotamide compared to placebo on the number and overall severity of migraine attacks experienced during a three-month treatment period together with associated symptoms.		
Methodology: Double-blind, placebo-controlled efficacy and safety study using a cross-over design.		
Number of subjects (planned and analyzed): Sixty-two (62) patients with migraine with aura.		
Diagnosis and main criteria for inclusion: Male and female patients with migraine with aura between 18 and 65 years old.		
Test product, dose and mode of administration, batch number: • Plactidil tablets containing 300 mg picotamide (batch no: 1102 (2012), F003Y (2015)) The study medication was given orally twice daily Reference therapy, dose and mode of administration, batch number: • Tablets containing placebo (batch no. D006W (2012), K037X (2015)) The study medication was given orally twice daily		
Duration of treatment: Plactidil: Twelve weeks oral administrations of the study medication. Placebo: Twelve weeks oral administrations of the study medication. Wash-out period of 4 weeks with placebo between treatment periods.		

Name of Sponsor/Company: **Proreo Pharma Innovation AG**		
***Name of Finished Product*:** **Plactidil**		
***Name of Active Ingredient*:** **Picotamide**		

Criteria for evaluation:
Efficacy:
- Mean number of auras during each treatment period,
- Mean number of migraine headache days in each treatment period,
- Mean number of non-migraine related headache days in each treatment periodMean number of auras followed by headache in each treatment period,
- Mean number of headache days in each month of treatment in each treatment period,
- Mean number of auras and/or migraine headache during each treatment period,
- Mean number of migraine headache attacks in each treatment period,
- Mean monthly consumption of rescue medication during the last month and the whole of each treatment period from the baseline period to Month 3,
- Mean duration of auras in each treatment period,
- Mean number of symptoms associated with auras in each treatment period,
- Reduction in the number of auras and the number of migraine headache days relative to the placebo treatment period.

Safety:
Incidence of all adverse events (AEs), serious AEs and AEs leading to withdrawal of trial medication, clinical laboratory tests, vital signs and physical examination.

Efficacy:
Not applicable.

Statistical methods:
Wilcoxon signed rank test on efficacy parameters.
Individual data listings and, if appropriate, descriptive statistics on safety data.

Results:

Efficacy Results:
- Picotamide did not reduce the number of auras in patients with migraine with aura compared to placebo in a larger patient population with 1 or more MwA attacks.
- Picotamide had no effect on the number and overall severity of migraine attacks experienced during a three-month treatment period together with associated symptoms compared to placebo in a larger patient population with 1 or more MwA attacks.
- Post hoc analysis indicates:
  - Based on rationales (IHS guidelines and based on recent Phase II clinical studies in migraine), subsets of patients with 1 - 6 and 3 - 6 MwA attacks per month prior to the study were analyzed.
  - When applying these selected inclusion criteria picotamide treatment was associated with a significant reduction of number of MwA attacks in comparison to placebo.
  - Number of MwA attacks in pre-study, as selection criterion for a migraine study, has an impact on clinical outcome.
- Instead of a cross-over design with an inclusion criteria of >1 MwA attacks per month, a parallel-group design with a solid run-in period with diary-controlled attack frequency as well as defining cut-offs (min-max) for number of MwA attacks per month may be more appropriate

Safety Results:
- Single and repeated oral doses of picotamide were well tolerated by the patients with migraine with aura;
- Three serious adverse events were reported; they were not regarded as related to the study medication;
- The majority of adverse events reported were mild. There were no differences in the incidence and the profile of the most relevant and frequent AEs between placebo and picotamide;
- There are two events of accidental bleeding for which a relationship to picotamide treatment cannot be completely excluded.

Date of the report: Juine 06, 2018