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Date: 22SEP2017



15-HMedIdeS-08

Eudract No: 2016-000249-30

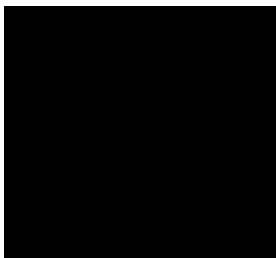
Statistical Analysis Plan

Final 1.0

Statistical Analysis Plan

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A PHASE II PILOT STUDY TO EVALUATE THE SAFETY, TOLERABILITY,
EFFICACY, PHARMACODYNAMICS AND PHARMACOKINETICS OF IDES
IN ASYMPTOMATIC ANTIBODY-MEDIATED THROMBOTIC
THROMBOCYTOPENIC PURPURA (TTP) PATIENTS WITH LOW ADAMTS13
ACTIVITY

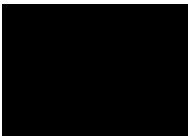


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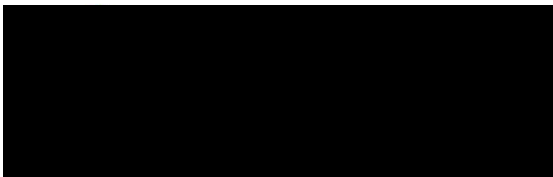
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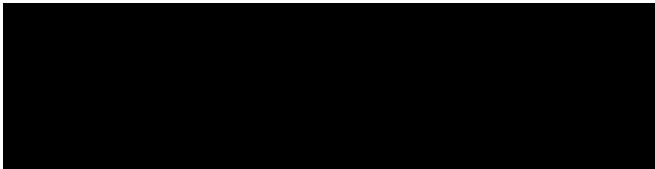
Author:

Date: 22 SEP 2017

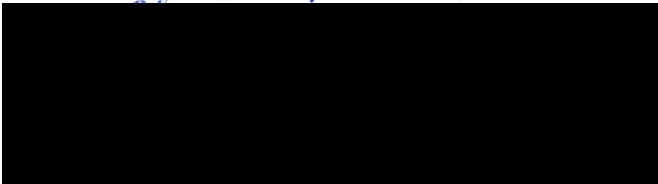


Reviewed and approved by:

Date: 22 SEP 2017



Date: 22 Sep 2017



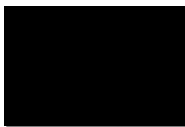


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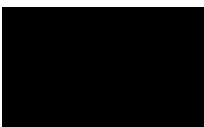
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1 Introduction

The purpose of this SAP is to describe in detail the planned statistical analyses and data presentations for the trial 15-HMedIdeS-08. The trial was exploratory in nature and was stopped prematurely by the sponsor after two subjects were included and evaluated. The reasons for the premature termination as given by the sponsor were: Hansa Medical decided, following an Internal Monitoring Committee meeting held on 19th of December 2016, that the study should be prematurely stopped. The decision was made following Hansa Medical's review of initial results from the study that demonstrated a non-favorable risk benefit profile in the first two patients.

Because of the premature termination of the trial and because the sponsor will no longer pursue the indication the analyses as described in the protocol (version 3, dated 21 June 2016) will not be performed. Instead, data collected for the two enrolled subjects will be listed and presented graphically.

1.1 Abbreviations and definition of Terms

Abbreviations	Meaning of abbreviations in document
ADAMTS13	a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13
[REDACTED]	[REDACTED]
ITT	Intention-to-treat
FAS	Full-Analysis Set
IMP	Investigational Medicinal Product
[REDACTED]	[REDACTED]
PP	Per-Protocol

1.2 Study Objectives and Endpoints

1.2.1 Primary objective

To assess safety and tolerability of single intravenous doses of IdeS in patients diagnosed with asymptomatic antibody-mediated TTP with low ADAMTS13 activity.

1.2.2 Secondary objectives

To determine the following in patients diagnosed with asymptomatic antibody-mediated TTP with low ADAMTS13 activity.

1. ADAMTS13 antigen, activity and antibody (IgG and F(ab')₂) levels following a single intravenous dose of IdeS during 64 days following IdeS dosing

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2. Serum concentration of IdeS following a single intravenous dose of IdeS
3. Pharmacodynamic (PD) profile as measured by IgG levels and F(ab')₂ fragments concentrations during 64 days following IdeS dosing
4. Immunogenicity profile of IdeS

1.2.3 Exploratory objective

To investigate the effect of IdeS on the levels of [REDACTED] and [REDACTED]

1.2.4 Primary endpoints

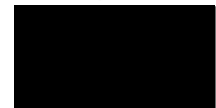
Primary Safety as measured by type, frequency and intensity of adverse events and change from baseline in parameters of clinical laboratory tests, vital signs and electrocardiograms (ECGs)

1.2.5 Secondary endpoints

- Change from baseline in ADAMTS13 activity and antibody levels (IgG and F(ab')₂).
- Time for ADAMTS13 activity to return to normal levels
- Number of cases with normalisation of ADAMTS13 at 64 days
- Serum concentration of IdeS
- Change from baseline in pharmacodynamics as measured by level of IgG and F(ab')₂ fragments
- Immunogenicity of IdeS by measuring anti-drug antibodies

1.2.6 Exploratory endpoints

- Change from baseline of [REDACTED] after IdeS dosing

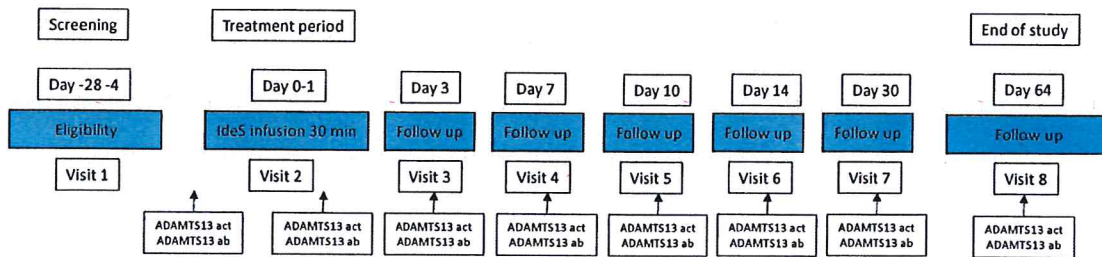


2 Study design

The trial is a phase II single arm trial in asymptomatic antibody-mediated thrombotic thrombocytopenic purpura (TTP) patients with low ADAMTS13 activity. Dosing was planned as 0.25 mg/kg for the first 3 patients followed by 0.50 mg/kg for the last 3 patients if the safety evaluation after the first 3 patients recommended to increase the dose.

The ongoing safety surveillance of the study resulted in termination of the study after the first two subjects were treated with IdeS infusion.

The overall schematic flow chart of the study is given below



2.1 Determination of Sample Size

Six patients were planned to be included but the enrolment was terminated after the first two patients.

2.2 Blinding

The study was not blinded.

2.3 Data Pre-processing

The data will be received from the data management database [redacted] and from the laboratories involved. Data will be converted into SDTM compliant SAS datasets. Due to the termination of the study ADaM datasets will not be produced.

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3 Analysis Sets

Due to the premature termination of the study there will be no formal definition of analysis sets and all recorded data will be presented.

4 Statistical analyses and presentation of data

4.1 General considerations

The planned summaries and tabulations will not be produced because data from only two subjects were recorded. All data will be presented in listings and in addition profile plots when relevant.

4.2 Listings

The following listings will be made

1. Subject disposition
2. Demography and body measurements
3. Prior and Concomitant medication
4. Medical history
5. Exposure
6. Laboratory – PK
7. Laboratory – PD
8. Laboratory – safety
9. ECG
10. Vital signs

In order to ease overview of data, all listings will be sorted by parameter, subject, and time point.

4.3 Profile plots

Data which are recorded several times during the 64 days duration of the trial will be presented graphically. The plots will be by parameter with the two subjects shown in the same plots. For parameters where lower-upper ranges exist, observations which are outside normal ranges will be marked.

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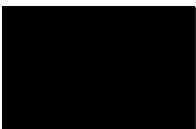
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5 Deviations from Protocol Analysis

The reporting of this trial deviates from the data presentations planned in the protocol because of the premature termination. No tabulations or analyses will be performed but all data will be shown in listings and when relevant in profile plots. The clinical trial report is planned to present the subset of all data which is relevant for an abbreviated report and efficacy section will not be included.

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6 Quality Control

Adequate quality control will be performed for the generation of the listings and profile plots to be constructed. The QC activities will follow  SOP 703 Programming of Single Use SAS Programs.


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7 Change Log

Edition	Effective on	Reason for revision
1.0	22 September 2017	New version