STUDY PROTOCOL

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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1. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study protocol.

Abbreviation	Explanation
ADA	Anti-drug antibody
ADAMTS13	**a d**isintegrin **a**nd **m**etalloproteinase with a **t**hrombo**s**pondin type 1 motif, member **13**
AE	Adverse event
APTt	Activated partial thromboplastin time
ATGAM	Equine anti-thymocyte globulin
AUC_t	Area under serum concentration time curve from t=0 to last timepoint
BMI	Body mass index
BW	Body weight
CKD	Chronic kidney disease
C_{max}	Maximum serum concentration
CRF	Case report form (electronic/paper)
CRO	Contract research organisation
CRP	C-reactive protein
CSR	Clinical study report
CTCAE	Common toxicity criteria for adverse events
CV	Coefficient of variation
DLT	Dose Limiting Toxicity
[redacted]	[redacted]
ECG	Electrocardiogram
EOS	End of study
FAS	Full analysis set
FRET	Fluorescence resonance energy transfer
GCP	Good clinical practice
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HR	Heart rate
ICF	Informed consent form
ICH	International conference on harmonisation
IdeS	Immunoglobulin G-degrading enzyme of *Streptococcus pyogenes*
IMC	Internal Monitoring Committee
IMP	Investigational medicinal products

Abbreviation	Explanation
IUD	intrauterine device
IUS	intrauterine system
IVIg	Intravenous immunoglobulin
[redacted]	[redacted]
MAHA	microangiopathic haemolytic anemia
MedDRA	Medical dictionary for regulatory activities
MSD	Meso Scale Diagnostic
NOAEL	No observed adverse effect level
PBS	Phosphate buffered saline
PD	Pharmacodynamics
PE	Plasma Exchange
PK	Pharmacokinetics
PK (INR)	Prothrombine complex (internationally normalised ratio)
PPS	Per protocol set
PRA	Panel reactive antibody
rATG	Rabbit anti-thymocyte globulin
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Serious adverse reaction
SOC	System organ class
SUSAR	Suspected unexpected serious adverse events
TEAE	Treatment emergent adverse event
TTP	Thrombotic thrombocytopenic purpura
vW	von Willebrand factor

2. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

2.1 Medical Emergencies Contacts

The principal investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. A medical emergency usually constitutes a serious adverse event (SAE) and is to be reported as such.

Name	**Role in the study**	**Telephone number & Mail address**
[redacted]	Principal Investigator	[redacted]
[redacted]	Medical Safety Officer	[redacted]
Elisabeth Sonesson	Sr. Clinical Research Manager	[redacted] elisabeth.sonesson@hansamedical.com

3. INTRODUCTION

3.1 Disease and Patient population

Thrombotic thrombocytopenic purpura (TTP) is a rare life-threatening thrombotic disorder of the blood-coagulation system, causing extensive microscopic clots to form in the small blood vessels throughout the body. These small blood clots, called thrombi, can damage many organs including the kidneys, heart and brain. TTP is a medical emergency that is almost always fatal if appropriate treatment is not initiated promptly. Treatment with plasma exchange (PE) and glucocorticoids reduces the mortality to between 10% and 15% (George 2012).

In the majority of patients, TTP is a result of autoantibody-mediated inhibition of a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13). This type of TTP is called acquired TTP. In a minority of patients, TTP is due to deleterious mutations in ADAMTS13; i.e., hereditary or congenital TTP.

Acquired TTP is characterized by thrombocytopenia and microangiopathic haemolytic anemia (MAHA) without an obvious cause, and may include fever, mild renal failure, and neurologic deficits (Sayani and Abrams 2015). The majority of the patients suffering from acquired TTP develop autoantibodies that bind and neutralize the proteolytic activity of ADAMTS13 and/or accelerate its clearance *in vivo* (Scheiflinger, Knöbl et al. 2003). Recently published data suggest that depletion of ADAMTS13 antigen, rather than enzyme inhibition, is the dominant pathogenic mechanism in acquired TTP (Thomas, de Groot et al. 2015). A severe deficiency of plasma ADAMTS13 activity (less than 5%) and the presence of autoantibodies are considered to be highly specific for the diagnosis of acquired TTP (Hovinga and Lämmle 2012). Anti-ADAMTS13 antibodies are present in the majority of patients (94–97%) suffering from acquired TTP and are considered to be strongly involved in the pathogenesis of the disease (Verbij, Fijnheer et al. 2014).

Early intervention improves prognosis dramatically. As a result, measurement of serum ADAMTS13 activity is not performed for diagnosis, as turn-around time tends to be long and awaiting results may delay life-saving treatment. However, measurement of ADAMTS13 and antibodies to ADAMTS13 are conducted for diagnostic confirmation.

3.2 Current Treatments

Due to the rarity of the disease very few randomized studies with definitive conclusions have been performed in TTP and its management is largely based on clinical experience (Verbij, Fijnheer et al. 2014). The mainstay of treatment is PE, while monitoring [redacted] and [redacted]. The ADAMTS13 assays may not be immediately available. Therefore, the treatment must be based on clinical symptoms and other laboratory tests and the decision to start PE should not wait for results of the ADAMTS13 assay (Sayani and Abrams 2015). In addition to plasma exchange, other methods are necessary to treat patients because of high frequency of relapse, especially in patients with high titre inhibitory antibodies. Most patients are treated with steroids and rituximab is part of standard therapy (Said, Haddad et al. 2014). Treatment must be started as soon as possible after diagnosis or even suspicion of TTP. [redacted], [redacted] level and ADAMTS13 results are indicators of disease severity and forms the basis for treatment decision. Immunosuppressive therapies like corticosteroids, anti-CD20 or cyclosporine are also being used in the treatment of acquired TTP.

3.2.1 Plasma Exchange

The mortality rate of TTP prior to the use of PE was approximately 90 percent but is now down to 15 percent or less (Sayani and Abrams 2015). PE is the standard treatment in acquired TTP and is considered to remove circulating antibodies to ADAMTS13 and the subsequent plasma replacement, replenish the deficient ADAMTS13 (Verbij, Fijnheer et al. 2014). Despite the rarity of TTP, these patients are the single largest consumers of plasma, with an average volume per episode of 40 L (Scully 2014). PE is performed once or twice daily until the [redacted] has recovered. Complications associated with plasma exchange (incidence 10%) are mostly related to the use of central venous catheter and the plasma replenishment (Said, Haddad et al. 2014).

According to the 2012 American Society of Apheresis Consensus Conference on TTP, response is defined as a [redacted] of at least 150 000/mL for 2 consecutive days, a normal or near normal [redacted], and stable or improving neurologic symptoms. The number of treatments needed varies, and may be higher in patients with high antibody titre (Sayani and Abrams 2015).

3.2.2 Steroids

Glucocorticoids are used in the acute management of acquired TTP and should be started directly together with PE (Sayani and Abrams 2015). Steroids are used to target the autoimmune component of the disease and are believed to suppress the production of anti-ADAMTS13. The effect of steroids may also be due to down-regulation of various cytokines involved in TTP pathogenesis (Verbij, Fijnheer et al. 2014).

3.2.3 Rituximab

Anti-CD20 (rituximab) was initially used in patients with a suboptimal response to standard treatment, such as those with refractory or relapsed disease (Verbij, Fijnheer et al. 2014) but is now standard of care as up-front treatment. Anti-CD20 therapy has been demonstrated to be effective in prolonging the duration of remission as well as decreasing the frequency of remission (Scully, McDonald et al. 2011).

3.3 IdeS

Immunoglobulin G-degrading enzyme of *Streptococcus pyogenes* (IdeS) is an IgG specific endopeptidase. Cleavage of IgG generates one $F(ab')_2$- and one homodimeric Fc-fragment and efficiently neutralizes Fc-mediated activities of IgG (HMed doc. No. 2012-003) (von Pawel-Rammingen, Johansson et al. 2002, Wenig, Chatwell et al. 2004, Vincents, von Pawel-Rammingen et al. 2004). IdeS-mediated IgG degradation constitutes a novel therapeutic principle for the treatment of IgG-driven human diseases.

Hansa Medical AB has performed *in vitro* studies and clearly demonstrated that IdeS effectively cleaves purified IgG as well as IgG in serum from human and rabbit. IdeS is very specific in that no other substrate has been found (HMed Doc. No. 2012-003).

3.4 IdeS Clinical Studies

A phase I study first in man single ascending dose study in 29 healthy subjects showed that IdeS was safe and well tolerated in doses up to 0.24 mg/kg body weight (BW). The study demonstrated that IdeS could be administered at 0.24 mg/kg BW with a favourable safety profile. It also showed that IdeS could effectively reduce the levels of plasma IgG and that newly synthesised IgG was not detectable until two weeks after dosing. At the two highest

doses, 0.12 and 0.24 mg/kg BW, IdeS completely cleaved the pool of plasma IgG within 14 minutes after initiation of infusion and the level of intact IgG was reduced to less than 5% of its original level. In addition, newly synthesized IgG was not detectable until two weeks after dosing (HMed Doc. No. 2014-003). The data clearly indicates that a single dose of IdeS is superior to both plasmapheresis and immunoadsorption with respect to efficiency and rate of plasma IgG reduction. Since IdeS degrades IgG there was concern that study subjects would have an increased risk of infection and that subclinical infections (e.g., pneumococci) would pose a problem. Therefore, subjects received antibiotic prophylaxis until plasma IgG levels had returned to levels $\geq$4.5 g/L and there were no signs of an increased rate of infections within the study group. The adverse events that were reported, none of which were reported as serious, were as anticipated from to the biological nature of the drug. Hence, headache and fatigue were more common in the IdeS treated subjects compared to placebo. One possible infusion reaction was reported among the placebo treated subjects and one among the IdeS treated, the latter resolved within 60 minutes after treatment with antihistamine and glucocorticoids and the infusion was completed. All adverse events were mild or moderate.

One phase II study was completed at Uppsala University Hospital, Sweden in March 2015. The study was a single arm study with ascending doses of IdeS in 8 chronic kidney disease (CKD) patients on the kidney transplantation waiting list and sensitized to human leucocyte antigens (HLAs). The patients enrolled were diagnosed with CKD, in dialysis and on the waiting list for a kidney transplant. However, transplantation was not part of the study protocol. The study showed that one or two doses of IdeS at 0.25 mg/kg BW in the majority of the patients resulted in HLA antibody levels, acceptable for transplantation within 24 hours from dosing. In addition, in all patients having a significant pre-dose panel-reactivity the percentage panel reactive antibody (PRA) was reduced one hour after IdeS treatment. It was also concluded that in the majority of patients the complement dependent cytotoxic crossmatches were converted to negative already one hour after a single dose of IdeS (0.12 or 0.25 mg/kg BW) and the crossmatches remained negative for one week. There were a total of five SAEs reported in the study of which four were classified as probable or possible related to study drug, i.e., suspected serious adverse reactions (SARs). Three of the SARs were infections and one myalgia. Two phase II studies using IdeS in sensitized patients prior to kidney transplantation are currently ongoing in Uppsala, Sweden and Los Angeles, US.

3.5 Overdose

An overdose is a dose in excess of the dose specified in the protocol. There are no data on overdosing of IdeS. There is no known antidote but depletion of IgG can be restored with intravenous immunoglobulin (IVIg). In the event of an overdose the patient should be monitored closely and treated symptomatically. This should be recorded as follows:

- An overdose with associated adverse events (AEs) is recorded as the AE diagnosis/symptoms on the relevant AE modules in the case report form (CRF)

- An overdose without associated symptoms is only reported in the patient file

3.6 Study Rationale and Discussion on Overall Study Design

Asymptomatic patients with low ADAMTS13 activity are at significant risk of relapse. Patients may never have recovered a normal ADAMTS13 activity after the acute episode, or more commonly, ADAMTS13 activity may fall in remission, predisposing to clinical relapse. Elective rituximab is used in this situation to clear anti-ADAMTS13 antibodies and normalise ADAMTS13 activity, thus reducing the risk of a clinical relapse. It is possible that addition of IdeS will be an advantage in asymptomatic patients by quickly removing ADAMTS13 antibodies from circulation, thus allowing ADAMTS13 to return to normal levels.

The primary objective of the proposed pilot study is to monitor safety and tolerability in patients diagnosed with asymptomatic antibody-mediated TTP with low ADAMTS13 activity after receiving single intravenous doses of IdeS. The secondary objective is to investigate IdeS efficacy in significantly increasing ADAMTS13 activity and decreasing ADAMTS13 antibody levels in patients with asymptomatic antibody-mediated TTP. In the current study this will be investigated in asymptomatic patients with reduced levels of ADAMTS13 activity and measurable levels of circulating ADAMTS13 antibodies.

Eligible patients must have ADAMTS13 activity levels less than 10% of normal levels. Each patient will receive one dose of 0.25 mg/kg BW IdeS. Following an evaluation of safety and efficacy in 3 patients dosed at 0.25 mg/kg, there will be a possibility to increase the dose to 0.5 mg/kg for the next 3 patients. The dose will be given as a single intravenous infusion (for details see section 7, Study conduct). Single doses up to 0.24 mg/kg BW (maximum dose tested) has previously been given to healthy volunteers and doses up to two times 0.25 mg/kg BW has been given to CKD patients. In asymptomatic patients with acquired TTP it is expected that the pharmacokinetic of IdeS pharmacokinetics is similar to healthy subjects.

Based on the current knowledge, including experience from completed and ongoing clinical studies, it is expected that IdeS will degrade IgG into $F(ab')_2$ and Fc fragments across all compartments allowing a rapid and potent reduction of the specific anti-ADAMTS13 antibodies. The $F(ab')_2$-fragment created by IdeS treatment will not be able to clear ADAMTS13 via Fc-mediated activities. However, the remaining $F(ab')_2$ seen in serum after 24-48 hours may still have the capacity to block ADAMTS13 activity for example by interfering with binding to von Willebrand (vW) factor. However, as shown by Thomas et. al. (Thomas, de Groot et al. 2015) depletion of ADAMTS13 antigen, rather than enzyme inhibition, is the dominant pathogenic mechanism in acquired TTP.

The hypothesis is that the reduction in anti-ADAMTS13 IgG will translate into a rise in ADAMTS13 activity and hence reduce the risk of clinical relapse.

3.7 Risk/Benefit and Ethical Assessment

A starting dose of 0.25 mg/kg BW has been selected for this study. The phase I study did not identify any dose limiting factors even at the highest tested dose (0.24 mg/kg BW) and CKD patients in a completed phase II study in Sweden were exposed to a total dose of 0.5 mg/kg BW with acceptable safety profile. In addition, the doses of 0.25 mg/kg and 0.5 mg/kg BW are well covered by the no observed adverse effect level (NOAEL) of 2.0 mg/kg BW obtained in toxicology studies. The pharmacokinetics (PK) of IdeS in asymptomatic TTP patients is expected to be similar to what is observed in healthy subjects, thus, a starting dose of 0.25 mg/kg BW is considered to be safe.

[redacted]

[redacted]

Since IdeS effectively removes the IgG pool, there may be an increased risk of infection. In order to minimise the risk for bacterial infections all patients treated with IdeS will receive a two-week regimen of prophylactic antibiotics following IdeS dosing. Patients will be screened for viruses (Hepatitis B, C and human immunodeficiency virus [HIV]) and on-going infections and patients having clinical signs of on-going infections will be excluded from the study. Patients will be instructed to contact the principal investigator immediately if they have any sign of infection. In case of infection in a patient with low IgG plasma levels, intravenous immunoglobulin may be indicated.

It has been demonstrated in laboratory studies that IdeS cleaves biologics based on human IgG including; IVIg, basiliximab, rituximab, adalimumab, denosumab, belatacept and etanercept. IdeS also cleaves rabbit anti-thymocyte globulin (rATG) but not equine anti-thymocyte globulin (ATGAM). The optimal interval between HMedIdeS administration and these biologics have not been defined (HMed Doc. No. 2012-003). Rituximab is cleaved by IdeS and therefore rituximab treatment within 7 days prior to IdeS dosing will not be allowed in TTP patients. The concomitant use of these other biologics and IdeS will continue to be closely monitored in order to mitigate any changes in the efficacy of these biologics.

To date, there have been 3 reports of myalgia in completed studies, 1 was serious and unexpected and occurred in a patient with a previous history of myalgia to atorvastatin who was on chronic glucocorticoid treatment. The remaining 2 were non-serious. The non-serious cases resolved and the serious case was improving upon steroid tapering. Of note, an extensive workup including muscle biopsy, electromyograms and other muscle related biomarkers showed no abnormalities. Myalgias have been reported with treatment

with other biologics such as IVIg and rituximab (Orbach et al., 2005, Rituximab Summary of Product Characteristics).

Creatine kinase (CK) levels will be assessed in this study.

The patients will be closely monitored for all adverse events. The principal investigator must make sure that sufficient facilities and procedures are available to handle emergency situations during the study. The University College London Hospitals has extensive experience in early phase studies and there are adequate procedures in place to handle unexpected adverse reactions.

4. STUDY OBJECTIVES AND ENDPOINTS

4.1 Objectives

4.1.1 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

4.1.2 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
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

4.1.3 Exploratory Objectives

[redacted]

4.2 Endpoints

4.2.1 Primary Endpoint

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)

4.2.2 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

4.2.3 Exploratory Endpoints

- [redacted]

5. STUDY DESIGN

5.1 Overall Study Design

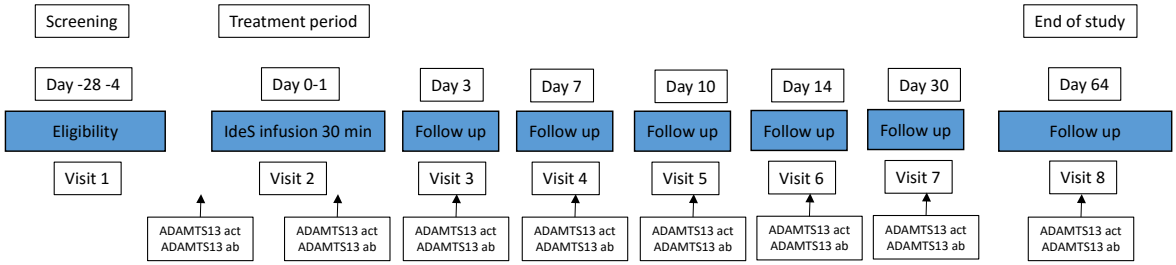


Figure 1. Overall schematic study design

This is a phase II, single arm study. The primary objective of the study is to assess safety and tolerability of IdeS in asymptomatic patients diagnosed with acquired TTP in clinical remission with ADAMTS13 activity less than 10% of normal levels. Secondary objectives include monitoring of ADAMTS13 activity and levels of ADAMTS13 antibodies. In addition, IdeS serum concentration, PD (total IgG and $F(ab')_2$ fragment concentrations) and immunogenicity profile of IdeS will be assessed.

Patients will be treated at the College University London Hospital, and will be subject to a single 30 minutes infusion with IdeS on day 0. Blood sampling for safety and efficacy will be performed and the patient will be closely monitored over a 24 h period after infusion after which they will be discharged. The follow-up visits will be in the out-clinic setting. Patients will receive premedication with paracetamol, Solu-Medrol and Loratidine before IdeS infusions. All patients will also receive a two-week regimen of prophylactic antibiotics starting pre-dose.

Following an evaluation of safety (clinical chemistry, haematology and coagulation and AEs) and efficacy in 3 patients receiving 0.25 mg/kg there will be a potential to increase the IdeS dose to 0.5 mg/kg for the remaining 3 patients.

5.2 Planned Number of Trial Sites and Subjects

The study will be conducted at one site, University College London Hospital, UK and will include 6 asymptomatic patients diagnosed with acquired TTP.

5.3 Decision Criteria for Dose Escalation

The decision for dose escalation to 0.5 mg/kg BW or an intermediary dose will be taken after the first 3 patients have been administered a dose of 0.25 mg/kg BW. The decision to escalate the dose will be a consensus between the Principal Investigator and the Sponsor. The safety, tolerability and efficacy of the dose will be evaluated prior to dose escalation. An internal monitoring committee (IMC) at Hansa Medical will review available safety and tolerability data after 3 patients have received a dose of 0.25 mg/kg before proceeding to the next dose. Safety data collected up to and including day 14 will be evaluated. The safety data will be compiled in an IMC package and also sent to the Principal Investigator for review. Safety data available for evaluation by the IMC and Principal Investigator before a dose escalation decision is shown in Table 3. In addition, ADAMTS13 activity,

ADAMTS13 antibodies and [redacted] will be included in the evaluation of a dose escalation. There will be at least 14 days between dosing of the first patient in a higher dose group and dosing of the last patient in the previous dose group.

If a Dose Limiting Toxicity (DLT) is demonstrated in one patient who has received a dose of 0.25 mg/kg BW and the underlying AE(s) is at least possibly related to the investigational drug, dose escalation will not occur and 3 additional patients will be administered 0.25 mg/kg. A well-tolerated 0.25 mg/kg dose may also be administered to the next three patients entered in the study if the pharmacodynamics effect of the dose is judged as satisfactory. A dose of 0.5 mg/kg BW or an intermediate dose may be given in the next three patients, if considered safe by the Principal Investigator and the Sponsor.

5.4 Definition of Dose Limiting Toxicity (DLT)

A significant reduction of total IgG levels in serum is a desired effect of IdeS treatment and is not considered a DLT. Any novel AE (including infusion reactions) with a Common Toxicity Criteria for Adverse Events (CTCAE) v.4.0 grade 3 or more and with a possible relationship to the investigational drug is considered a DLT (see Appendix 1 for CTCAE v. 4.0).

5.5 Internal Monitoring Committee

An IMC will be formed and will be convened to assess safety data on each patient enrolled in the study. If at any time in the study, 2 or more patients have experienced a Grade 3 of related adverse event (NCI CTCAE v 4.0), the IMC will be convened. The IMC will also review a safety data package (Table 3) prior to dose escalation. An IMC charter will be written to pre-specify roles, responsibilities, procedures, and deliverables, as well as the purpose, scope, and timing of meetings.

6. PATIENT SELECTION CRITERIA

6.1 Study Population

6.1.1 Inclusion Criteria

For inclusion in the study patient must fulfil the following criteria.

1. Ability to understand and must sign the informed consent form

2. Age 18 years or above

3. Patients diagnosed with acquired TTP with ADAMTS13 levels of ≤ 10 % in clinical remission and with measurable or previously confirmed ADAMTS13 antibodies

4. Females of childbearing potential and males must use highly effective contraception during the study and at least for 12 weeks after IdeS dosing

   Highly effective contraception methods include:

   1. Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception

   2. Female sterilisation (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment

   3. Male sterilisation (at least 6 months prior to screening). For female subjects in the study, the vasectomised male partner should be the sole partner for that subject

   4. Combination of any two of the following methods (a+b or a+c or b+c):

      a) Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception

      b) Placement of an intrauterine device (IUD) or intrauterine system (IUS).

      c) Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

   In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment. Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks prior to screening. In the case of oophorectomy alone, only when the reproductive

status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

6.1.2 Exclusion Criteria

Patients must not enter the study if any of the following exclusion criteria are fulfilled

1. Prior malignancy within 5 years excluding adequately treated basal cell or squamous cell skin cancer, cervical carcinoma in situ

2. Any positive result on screening for serum hepatitis B surface antigen, hepatitis C antibody and HIV

3. Clinical signs of ongoing infectious disease. This includes P-C-reactive protein (CRP) >10.

4. Tested positive for IgE antibodies against IdeS as measured by ImmunoCap.

5. No secondary cause of TTP

6. Rituximab treatment or other antibody-based therapy within 7 days prior to IdeS dosing

7. Treatment with investigational medicinal product within the last 12 weeks preceding screening or longer if judged by the investigator to possibly influence the outcome of the current study

8. Severe other conditions requiring treatment and close monitoring, e.g. cardiac failure $\geq$ NYHA (New York Heart Association) grade 3, unstable coronary disease or oxygen dependent COPD

9. History of any other clinically significant disease or disorder which, in the opinion of the investigator, may either put the patient at increased risk because of participation in the study, or influence the results or the patient's ability to participate in the study

10. Hypogammaglobulinemia defined as any values of P-total IgG less than 3 g/L

11. History of severe allergy/hypersensitivity or ongoing allergy/hypersensitivity, as judged by the investigator or history of hypersensitivity to drugs with a similar chemical structure or class to IdeS (e.g., streptokinase and/or staphylokinase)

12. Substance abuse or other concurrent medical condition that, in the investigator's opinion, could confound study interpretation or affect the patient's ability to tolerate or complete the study

13. Investigator considers patient unlikely to comply with study procedures, restrictions and requirements

14. Breast feeding women or women with a positive pregnancy test

15. Previously received IdeS treatment

6.2 Restrictions

Patients should abstain from drinking alcoholic beverages for 72 hours before the screening visit and all subsequent visits to the clinic. In addition, patients should abstain from alcoholic beverages during the residential stay.

The patients should abstain from strenuous physical activity that is not within the patient's normal weekly routine for 48 h prior to any visit until the end of study.

Patients must not participate in another clinical study during the course of the present study.

6.3 Withdrawal and Discontinuation

6.3.1 Criteria for Discontinuation from the Study

Patients may be discontinued from study treatment and assessments at any time. Specific reasons for discontinuation can be:

- Voluntary discontinuation by the patient who is at any time free to discontinue his/her participation in the study, without prejudice to further treatment
- Risk to patients as judged by the investigator and/or sponsor
- Severe non-compliance to protocol as judged by the investigator and/or sponsor
- Incorrectly enrolled patients
- Patient lost to follow-up
- Adverse events
- Withdrawal of informed consent to the use of biological samples may be a reason for withdrawal of a patient

Patients who are withdrawn from the study by the investigator due to adverse events will not be replaced. Patients who withdraw for reasons other than adverse events may be replaced. A replacement patient must be an eligible patient according to the protocol and inclusion will follow the procedures described in this protocol.

6.3.2 Procedures for Discontinuation of a Patient from the Study

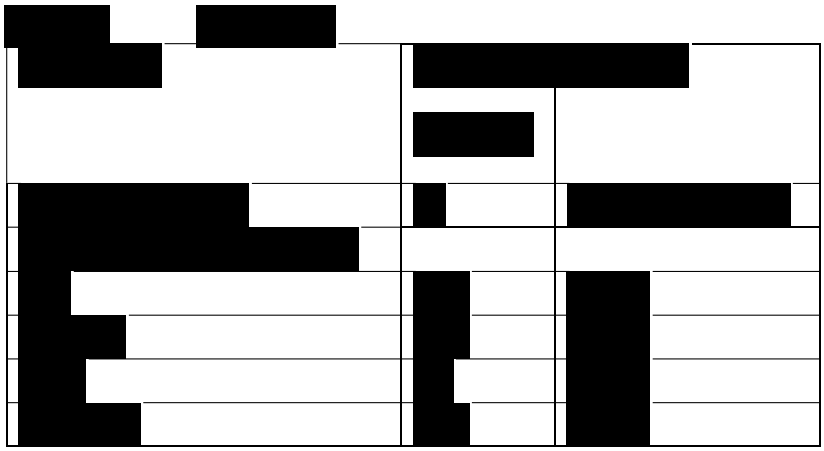
A patient who discontinues after study drug administration will always be asked about the reason(s) for discontinuation and the presence of any adverse events. If possible, they will be seen and assessed by an investigator(s). Adverse events will be followed until they resolve, stabilize or the clinical outcome of the patient is ascertained. If possible, patients who discontinue from the study before completion should undergo the assessments and procedures scheduled for the end of study follow up visit. Patients who, for a medical reason, cannot comply with the protocol procedures will be followed by best procedure, e.g., telephone call, to retrieve safety and efficacy data.

7. STUDY CONDUCT

7.1 Study Treatment

7.1.1 IdeS

IdeS is a clear colourless liquid. It is formulated at 10 g/L in phosphate buffered saline (PBS) and intended for intravenous infusion after dilution. Refer to Table 1 for composition.



7.1.2 Storage and Handling

All patients will receive treatment with IdeS. IdeS will be supplied to the hospital pharmacy by [redacted] in 7 mL vials packed into cartons containing 10 vials each. Vials should be kept dark at - 20°C. IdeS infusion solution will be prepared by pharmacy staff at the study unit. Administration will be performed using an infusion syringe or infusion bag with a filter containing infusion set and an infusion pump. Details on preparation, labelling and administration of IdeS are described in the pharmacy manual.

7.1.3 Packaging and Labelling

Packaging and labelling of the investigational medical product (IMP) will be performed in accordance with GMP and national regulatory requirements. The IMP will be labelled according to Annex 13, EudraLex Volume 4 and national regulatory requirements.

7.1.4 Drug Accountability and Compliance Check

The administration of all medication (including investigational products) must be recorded in the appropriate sections of the CRF. Treatment compliance will be assured by supervised administration of the investigational product by the investigator or delegate. The dose, date and time of administration of the investigational product will be checked by the monitor at monitoring visits.

It is the principal investigators/institution's responsibility to establish a system for handling study treatments, including investigational medicinal products, to ensure that:

1. Deliveries are correctly received by a responsible person (e.g., pharmacist or designated study personnel)

2. Deliveries are recorded

3. Study treatments are handled and stored safely and properly

4. The study drug provided for this study will be used only as directed in the study protocol

5. The study personnel will account for all drugs dispensed and returned. Any discrepancies must be documented, investigated and appropriately resolved

6. At the end of the study, the pharmacy personnel will account for all unused drugs and for appropriate destruction/return of all unused drugs to the sponsor for destruction. Certificates of delivery, destruction and return must be signed by a study team member.

7.1.5 Administration of IMP

An intravenous dose of IdeS will be administered over 30 minutes. Each patient will receive a single dose of 0.25 or 0.5 mg/kg BW. Detailed instructions on preparation and administration are provided in the pharmacy manual. The infusion may be slowed down or stopped and restarted if required.

7.2 Study Procedures

For each patient the duration of the treatment period including screening and follow up visits will be approximately 3 months. Timing (45 min, 2 h, 6 h and 24 h respectively as indicated in the flow chart in Table 2) of sampling on day 0 relates to start of infusion.

Visit 1 (Screening Day -28 – 4)

All patients considered for the study must give their written consent before screening or any other study procedure is performed. Screening of a patient can take place up to 28 days before the first dosing on study day 0. To be eligible for the study patients have to meet all inclusion criteria and no exclusion criteria. A patient failing screening may not be rescreened. However, if a patient has been screened and found eligible he or she can be rescreened if dosing could not be performed within 28 days due to logistical reasons.

At the screening visit each subject will be informed about the study and after signing the informed consent form assessments for eligibility will commence. The eligibility evaluation includes adherence to inclusion and exclusion criteria, collection of concomitant medication, demographic data and medical history. A full physical examination, height and weight measurements, vital signs including resting blood pressure, pulse, respiratory frequency, 12-lead resting ECG and body temperature will be measured. AEs that occur in the time period between informed consent and administration of the trial drug should be recorded as part of the patient's medical history, but will not be considered a treatment emergent adverse event (TEAE) unless directly related to study procedures (e.g., hematoma secondary to laboratory testing) or it meets the definition of an SAE.

Additionally, blood sampling for serology (HIV, hepatitis), pregnancy test, clinical chemistry (including [redacted] and immunoglobulins), haematology (including [redacted])

and urine sampling for urinalysis as well as blood samples for analysis of ADAMTS13 activity, ADAMTS13 antibodies, and anti-IdeS IgE will be collected.

Visit 2 (Residential stay Day 0 to Day 1)

Patients found eligible at the screening visit will be included in the study. At visit 2 an eligibility check will be performed pre-dose within 60 min prior to IdeS infusion (inclusion/exclusion criteria, medical history, concomitant medication, vital signs, body temperature, urinalysis, blood sampling for pregnancy test, safety laboratory parameters (including [redacted], [redacted] and immunoglobulins (IgG, IgM and IgA), ADAMTS13 activity, ADAMTS13 antibodies, [redacted], IdeS concentration, total IgG and F(ab')$_2$ fragment concentrations (PD) and ADA. Hydrocortison, paracetamol and antihistamine (chlorphenamine maleate) will be administered pre-dose to prevent/minimise risk of infusion reactions. Weight will be measured and prophylactic antibiotics will be administered.

Patients will receive a single intravenous dose of IdeS over 30 minutes.

At 2, 6 and 24 h post IdeS infusion blood sampling for determination of total IgG and F(ab')$_2$ fragment concentrations (PD), ADAMTS13 activity and antibodies, safety laboratory parameters, body temperature and [redacted] as well as urine sampling will be performed. Assessment of vital signs and ECG will be performed at 6 hours post dosing.

At 45 min, 2, 6 and 24 h post IdeS infusion sampling for determination of IdeS concentration will be performed.

AEs and concomitant medication will be recorded on the applicable CRFs throughout the visit.

Visit 3, 4, 5 and 6 (Days 3, 7, 10 and 14 respectively)

At visits 3, 4, 5 and 6 safety laboratory parameters, IdeS concentration, total IgG and F(ab')$_2$ fragment concentrations (PD), AEs and concomitant medication will be assessed as well as vital signs, ADAMTS13 activity, ADAMTS13 antibodies and [redacted]. Urine will be collected for urinalysis. Additionally, at visits 3, 4 and 6 ADA will be measured. Body temperature, weight and 12-lead resting ECG will only be measured at visit 6.

Visit 7 (Day 30)

At visits 7 safety laboratory parameters, total IgG and F(ab')$_2$ fragment concentrations (PD), AEs and concomitant medication will be assessed as well as vital signs, weight, body temperature, 12-lead resting ECG, ADAMTS13 activity, ADAMTS13 antibodies and [redacted]. A physical examination will be performed. Urine will be collected for urinalysis.

Visit 8 (End of Study, Day 64)

A follow-up visit will be performed 64 days following IdeS infusion. This will be considered the end of study for the patient. At this visit a physical examination will be performed and the patient will be assessed for vital signs, weight, body temperature, 12-lead resting ECG, AEs and concomitant medication. Blood sampling for analysis of safety laboratory

parameters, pregnancy test, ADAMTS13 activity, ADAMTS13 antibodies, [redacted], total IgG and F(ab')$_2$ fragment concentrations (PD) and anti-drug antibody (ADA) will be performed. Urine will be collected for urinalysis.

7.3 Study Flow Chart

Table 2. Study flow chart

Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
	Screening	Treatment period						EOS
Assessment/Day	-28 to -4	0-1	3	7	10	14	30	64
Informed Consent	x							
Demographics	x							
Medical history	x	x[b]						
Inclusion/exclusion	x	x[b]						
Physical examination	x						x	x
Weight	x	x[b]				x	x	x
Height	x							
Vital signs (blood pressure & pulse respiratory frequency)	x	x[a]	x	x	x	x	x	x
Body temperature	x	x[c]				x	x	x
Clinical chemistry (incl. immunoglobulins and [redacted]), haematology [redacted]. [redacted] urinalysis	x	x[c]	x	x	x	x	x	x
Serum pregnancy test	x	x[b]						x
ADAMTS13 activity	x	x[c]	x	x	x	x	x	x
ADAMTS13 antibodies	x	x[c]	x	x	x	x	x	x
Adverse events	x	x	x	x	x	x	x	x
12-lead ECG	x	x[a]				x	x	x
IdeS infusion		x						
Hydrocortison, paracetamol, antihistamine		x[b]						
Prophylactic antibiotic		x						
IdeS concentration (PK)		x[d]	x	x	x	x		
[redacted]		x[c]	x	x	x	x	x	x
PD sampling (IgG SDS-PAGE, IgG and F(ab')$_2$ concentration)		x[c]	x	x	x	x	x	x
ImmunoCAP IgG (ADA)		x[b]	x	x		x		x
ImmunoCAP IgE	x							
HIV, Hepatitis B and C	x							
Concomitant medication	x	x	x	x	x	x	x	x

[a]predose and 6 h post dose

[b]predose

[c]predose, 2 h, 6 h and 24 h post dose

[d]predose, 45 min (+/- 5 min), 2 h (+/- 15 min), 6 h (+/- 30 min) and 24 h (+/- 2 h) post dose

7.3.1 Recording of Data

The investigator will ensure that all data collected in the study are provided to the Sponsor. He/she ensures the accuracy, completeness, legibility and timeliness of the data recorded in the appropriate sections of the CRF and according to any instructions provided. The principal investigator will provide sponsor with all data produced during the study from the scheduled study assessments. He/she ensures the accuracy, completeness, legibility, and timeliness of the data reported to sponsor in the CRF and in all required reports. The study assessments are described in the sections below and the timing of these assessments are detailed in the study flow chart. Predose assessments should be performed within 60 minutes prior to dosing.

The timing priority order at a particular time point is:

1. Samples for ADAMTS13 activity and ADAMTS13 antibodies
2. [redacted], [redacted], Immunoglobulin (safety laboratory parameters)
3. Samples for IgG and $F(ab')_2$ concentration and samples for IdeS concentration
4. Vital signs
5. ECG

7.3.2 Patient Care After End of Study

All study patients will be followed up regularly according to the follow-up routines for TTP patients. The frequencies of outpatient visits will be adjusted individually to the state of patient health.

8. STUDY ASSESSMENTS

All sampling, shipping and analysing of laboratory samples will be detailed in the laboratory manual. All safety samples as well as [redacted], Immunoglobulins and [redacted] will be analysed using standard tests by HSL at University College London Hospitals, UK, unless otherwise stated in the respective sections below.

8.1 Assessments Related to Endpoints

8.1.1 ADAMTS13 Activity

Evaluation of the primary endpoint will be analysed using fluorescence resonance energy transfer (FRET) assay for ADAMTS13 activity. The results will be confirmed using a commercial chromogenic Technozym® ADAMTS-13 Activity ELISA. The tests will be performed at HSL at University College London Hospitals, UK. Samples will be drawn at the time points indicated in the study flowchart.

8.1.2 ADAMTS13 Antibodies

Evaluation of the primary endpoint will be analysed using an IgG ELISA. The results will be confirmed using a commercial chromogenic Technozym® ADAMTS-13 autoantibody ELISA. The tests will be performed at HSL at University College London Hospitals, UK. Samples will be drawn at the time points indicated in the study flowchart.

8.1.3 Vital Signs

Blood pressure (systolic and diastolic arterial pressure, including calculation of mean arterial pressure), pulse and respiratory frequency will be measured at time points indicated in the study flowchart.

Systolic and diastolic blood pressure will be measured after the patient has been in supine position for at least 5 minutes. All recordings will be performed using validated standard equipment. Clinically significant abnormal findings will be reported as AEs.

8.1.4 Adverse Events

AEs will be recorded during the trial period, from obtaining the informed consent to the follow-up visit. For further information on definitions and reporting of AEs and SAEs, see Section 8.4.

8.1.5 Clinical Laboratory Variables

8.1.5.1 Clinical Chemistry and Haematology

Blood samples for safety laboratory evaluations of clinical chemistry and haematology parameters (see Table 3) will be collected at the time-points indicated in the study flow chart. Actual sampling time will be recorded. Clinically significant abnormal findings will be reported as AEs. The clinical chemistry and haematology will be analysed locally.

8.1.5.2 Urinalysis

Urine samples (see Table 3) are taken at the time points indicated in the study flowchart. Samples will be analysed locally. In case of abnormal results, a microscopic test will be performed.

Table 3. The following safety laboratory variables will be measured

Clinical chemistry	**Coagulation**
P-Alanine aminotransferase	P-Activated partial thromboplastin time (APTt)
P-Albumin	P-PK (internationally normalized ratio [INR])
P-Alkaline phosphatase	
P-Aspartate aminotransferase	**Haematology**
P-Bilirubin, total	B-Haemoglobin
P-Bilirubin, indirect	B- Haematocrit
P-Calcium	B- Reticulocytes
P-Cholesterol	B- Neutrophils, lymphocytes eosinophils, and basophils
P-Creatine phosphokinase	B- White blood cell count with differential count
P-C-reactive protein	[redacted]
P-Creatinine	B- Red blood cell count
P- Gamma-glutamyltransferase	B- Monocytes, large unclassified cells
P-Glucose	Mean cellular volume
P-Potassium	Mean corpuscular haemoglobin content
P-Sodium	Mean corpuscular haemoglobin concentration
P-Magnesium	
P-Phosphorus	**Urinalysis**
P-haptoglobin	U-Glucose
P-triglycerides	U-Haemoglobin
P- troponin T	U-Protein
P-Urea (blood urea nitrogen)	U-bilirubin
P-IgG	U-pH
P-Total protein	U-Nitrite
P-Lactate dehydrogenase	U-Ketone
P-immunoglobulins (IgG, IgM and IgGA)	U-Urobilinogen

8.1.6 Electrocardiogram

The 12-lead ECG will be recorded with a validated ECG device. The parameters for heart rate (HR), PR interval, RR, QRS, QT and QTc(F) will be assessed (i.e., QT correction according to the Fridericia formula $QTcF=QT/RR^{0.33}$). ECG recordings will capture at least

four QRS complexes, i.e., evaluable RR intervals. The Investigator or designee will evaluate whether the ECG is normal or abnormal and whether it is clinically significant, if abnormal. Any occurrence or de- or re-polarization disorders, arrhythmic disorders or other abnormalities will be assessed and any changes compared to the baseline (i.e., predose, treatment day 0) record will be commented. Clinically significant abnormal findings will be reported as AEs.

Additional ECGs may be collected by the Investigator for safety reasons.

8.1.7 Pharmacodynamics

Samples for the determination of IgG and F(ab')$_2$ fragment levels (total and ADAMTS13 specific) in serum (PD) will be taken at the times presented in the study flow chart. The date and actual time of collection of each sample will be recorded on the laboratory requisition form and in the CRF. Samples will be analysed with electroluminescence based immunoassays using the MSD (Meso Scale Diagnostic) technology. The analyses will be performed at [redacted] Full details of the analytical method used and the analysis results will be detailed in a separate bioanalytical report.

8.1.8 Pharmacokinetics

Samples for determination of concentrations of IdeS in serum will be taken at the times presented in the study flow chart. The actual date and time of collection of each sample will be recorded on the laboratory requisition form and in the CRF. Samples will be analysed by an electroluminescence based immunoassay using the MSD technology. The analyses will be performed at [redacted]. Full details of the analytical method used and the analysis results will be detailed in a separate bioanalytical report.

8.1.9 Immunogenicity

Samples for the determination of anti-drug antibody (ADA) levels in serum will be taken at the times presented in the study flow chart. The date and time of collection of each sample will be recorded on the laboratory requisition form and in the CRF. Samples will be analysed for anti-IdeS IgG using a customized IdeS ImmunoCAP test, developed by [redacted] The analysis will be performed by [redacted] Full details of the analytical method used and the analysis results will be detailed in a separate bioanalytical report.

8.1.10 [redacted]

[redacted]

8.2 Other Assessments

8.2.1 ImmunoCAP anti-IdeS IgE

A sample for detection of anti-IdeS antibodies of IgE type will be taken at screening. The sample will be sent for analysis at [redacted] Full details of the analytical method used and the analysis results will be detailed in a separate bioanalytical report.

8.2.2 Demographics and Baseline Data

Information about gender, race, date of birth, body weight and height will be collected at the screening visit for each subject. Weight will also be recorded predose on the day of dosing as well as on day 14, 30 and 64. Measurements should be taken without shoes. Body mass index will be calculated from the height and weight. Medical history will be recorded at screening and at day 0.

8.2.3 Physical Examinations

A complete physical examination will be performed at screening, day 30 and on day 64 and include an assessment of the following: general appearance, head and neck (including ears, eyes, nose, mouth and throat), lymph nodes, abdomen, musculo-skeletal, cardiovascular, respiratory, gross neurological examination, skin and urinary system.

8.2.4 Body Temperature

Body temperature will be measured at screening and study visit 2. At visit 2/dosing, body temperature will be recorded pre-dose, 2, 6 and 24 hours post-dose as well as on days 14, 30 and 64.

8.2.5 Serology

Determination of HIV-1 and HIV-2 antibodies, hepatitis B surface-antigen and hepatitis C virus antibodies will be performed at screening for eligibility purposes.

8.2.6 Pregnancy Test

Serum β-hCG will be determined at screening, per-dose and at the end of study (EOS) visit, using validated standard methods.

8.2.7 Prior and Concomitant Medication

Information about prior and concomitant medication will be collected for each patient throughout the study.

8.2.8 Handling of Biological Samples

A detailed description of all sample collections and shipment procedures will be included in a separate laboratory manual. The sponsor or third part(ies) will store the blood samples for up to 2 years after reporting the trial.

8.3 Concomitant Medication

Therapeutic IgG based drugs such as Rituximab will be cleaved by IdeS during 7 days following dosing therefore Rituximab treatment within 7 days prior to IdeS dosing is not allowed (See Section 6.1.2). Other concomitant medication may be administered at the discretion of the Investigator. All concomitant medication, including premedication and prophylactic antibiotics will be recorded in the CRF, together with the main reason for its prescription.

8.3.1 Premedication

Patients will receive premedication with Solu-Medrol 250 mg i.v. and 10 mg loratadine p.o. before the IdeS infusion.

8.3.2 Prophylactic Antibiotic

All patients will receive a two-week regimen of Penicillin V (or alternatively Ciprofloxacin in case of allergy to penicillin) from the start of IdeS treatment.

8.4 Safety

It is of the utmost importance that all staff involved in the study is familiar with the content of this section. The principal investigator is responsible for ensuring this.

8.4.1 Definition of Adverse Events

An adverse event (AE) is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. Relationship to the study drug will be deemed as not related, unlikely, possible or probable. An undesirable medical condition can be symptoms (e.g., nausea and chest pain), signs (e.g., tachycardia and enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings and electrocardiograms).

In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

In case of a fatality, the cause of death is considered as the AE, and the death is considered as its outcome.

Pre-treatment Adverse Event

A pre-treatment adverse event is any untoward medical occurrence arising or observed between signing of informed consent and the first administration of the IMP.

Treatment Emergent Adverse Event

A treatment emergent adverse event is any AE occurring after the administration of the IMP and within the time of residual drug effect, or a pre-treatment adverse event or pre-existing medical condition that worsens in intensity after administration of the IMP and within the time of residual drug effect.

The time of residual drug effect is the estimated period of time after the administration of IMP, where the effect of the product is still considered to be present based on PK, PD or other substance characteristics. The residual dug effect is generally accepted to be 5 times the terminal half-life. Based on the data from healthy subjects, the terminal half-life of IdeS is expected to be approximately 5 days (mean of 118 hours in healthy subjects), i.e., in this study the residual drug effect is likely to be well within the 30 day visit.

Post-treatment Emergent Adverse Events

A post-treatment emergent adverse event is any event occurring after the time of residual drug effect of the IMP, i.e., from the visit on day 30.

8.4.2 Definition of Serious Adverse Events

A serious adverse event (SAE) is an AE or suspected adverse reaction (SAR) that is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Life-threatening event: An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Disability is defined as a substantial disruption in a person's ability to conduct normal life functions.

Hospitalization for inpatient hospitalization or prolongation of existing hospitalization.

- In this study for elective treatment of a pre-existing condition that did not worsen during the clinical investigation is not considered an AE. Hospitalisation for study drug dosing and observation as required by protocol is not considered an SAE. Admittance to an emergency room for observation without being admitted to the hospital may be considered to be an AE but is not considered as an SAE. However, complications that occur during hospitalization are AEs, and if a complication prolongs hospitalization, the event is considered serious.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events

include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

SAEs should be followed until the event resolves, stabilizes, or returns to baseline. If the patient is discontinued from the study prior to resolution/stabilization of the SAE, then the patient will be followed as part of the SAE/pharmacovigilance system.

8.4.3 Recording of Adverse Events

In clinical studies, an AE/SAE can occur at any time after signing of the informed consent until the end of the study, including run-in or washout periods, even if no study treatment has been administered, e.g., an AE can be related to a procedure in the protocol.

AEs will therefore be collected on the AE CRF from the time of signing of the informed consent and throughout the study period including the follow-up period. However, AEs that occur in the time period between informed consent and administration of the trial drug should be recorded as part of the patient's medical history, but will not be considered a treatment emergent adverse event (TEAE) unless directly related to study procedures (e.g., hematoma secondary to laboratory testing) or it meets the definition of an SAE.

8.4.4 Variables

The following variables will be recorded in the CRF for each AE; description of the AE, the date and time (if applicable) when the AE started and stopped, severity based on Common Toxicity Criteria grade (according to CTCAE v.4.0, see appendix 1) whether the AE is serious or not, causality rating, action taken with regard to investigational product, e.g., the AE caused patient to discontinue the study, and outcome.

For each reported AE the investigator will assess a causal assessment of the relationship of the event to study procedures and/or IdeS using the following criteria.

- **Unrelated:** applicable to an AE that occurs when the subject was not exposed to study treatment or another cause is obvious.
- **Unlikely to be related:** applicable to an AE that meets the following criteria
    - Does not follow a reasonable temporal sequence from study drug dosing
    - May readily have been produced by the patient's clinical state, environmental, or toxic factors, or other therapy administered to the patient
- **Possibly related:** applicable to AEs where connection with dosing of study drug appears unlikely but cannot be ruled out. Applicable to AEs where:
    - It follows a reasonable temporal sequence dosing with study drug
    - It follows a known pattern of response to study drug dosing (based on animal studies)

- **Probably related**: applicable to AEs that are considered, with a high degree of certainty, to be related to the study drug. Applicable to AEs where
    - It follows a reasonable temporal sequence study drug dosing
    - It cannot be reasonably explained by the know characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy
    - It follows a known patter of response to study drug dosing (based on animal data).
- For SAEs causal relationship will also be assessed for any study procedure.

8.4.5 Adverse Events Based On Signs and Symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel: "Have you had any health problems since you were last asked?" or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) rather than recording a list of signs and symptoms, for example: congestive heart failure rather than low ejection fraction, rales and dyspnea. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom not part of the diagnosis will be recorded separately, for example: congestive heart failure and conjunctivitis.

8.4.6 Adverse Events Based On Examinations and Tests

Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs and other safety variables will only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product. If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign/symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

Clinically relevant deterioration in non-protocol-mandated measurements will be reported as AE(s). Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (e.g., anaemia *versus* low haemoglobin value).

8.4.7 Follow-up of Unresolved Adverse Events

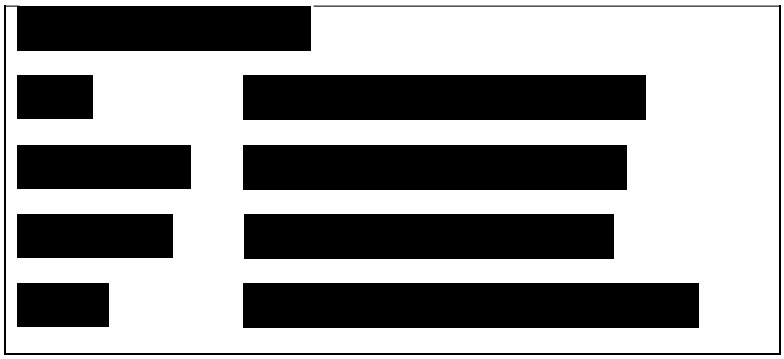
Any AEs that are unresolved at the patient's last AE assessment in the study are followed up by the investigator until stabilization, for as long as medically indicated or the overall clinical outcome of the patient is known, unless the patient is documented as "lost to follow-up". All SAEs and AEs leading to discontinuation should be followed until the event resolves, stabilizes, or returns to baseline.

Reasonable attempts to obtain this information must be made and documented. Sponsor retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

8.4.8 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the CRF. SAEs will be recorded from the time of informed consent.

All SAEs must be reported, whether or not considered related to the study drug, on a separate SAE Report Form. All SAEs will also be recorded in the CRF. An assigned contract research organisation ( ) will be responsible for reporting all SAEs to regulatory authorities and ethics committees in accordance with International conference on harmonisation (ICH) Good Clinical Practice and local regulations. As soon as the Investigator is aware of a potential SAE he/she should contact by fax or e-mail and in any case *no later than 24 hours* after the knowledge of such a case. At the time of initial reporting the investigator must provide as a minimum requirement, patient number, birth date, description of the SAE and a preliminary assessment of causality.



For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform the sponsor and monitor of any follow-up information on a previously reported SAE immediately but no later than within 24 hours of when he or she becomes aware of it. The monitor or sponsor will advise the investigator/study site personnel how to proceed.

The SAE reporting procedures are detailed in the study specific Safety Management Plan. This plan is an agreement between the sponsor, and .

8.4.9 Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

Suspected unexpected serious adverse reactions (SUSARs) must be reported to Regulatory Authorities. A suspected serious adverse reaction is any serious adverse event for which there is a reasonable possibility that the investigational product caused the adverse event. A serious adverse reaction is considered "unexpected" if it is not listed in the Reference Safety Information section of the investigator brochure or is not listed at the specificity or severity that has been observed.

SUSARs with an outcome of death or are life threatening must be reported to the relevant Regulatory Authorities within 7 calendar days, all other SUSARs must be submitted within

15 calendar days. The SUSAR reporting procedures are detailed in the study Safety Management Plan. This plan is an agreement between the sponsor, and [redacted]. The sponsor will notify the appropriate regulatory agency(ies) and all participating site Investigators of any SUSARs on an expedited basis and in accordance with applicable regulations. In addition, the sponsor is responsible for informing all investigators in all ongoing studies involving IdeS about all SUSARs.

It is the responsibility of the site Investigator to promptly notify the Ethics Committee and other appropriate institutional regulatory bodies of all SUSARs received involving risk to human subjects as per their applicable requirements.

9. BIOLOGICAL SAMPLING PROCEDURES

9.1 Volume of Blood

The maximum volume to be drawn from each patient in the study will not exceed 300 mL.

9.2 Handling, Storage and Destruction of Biological Samples

Safety samples will be used or disposed after analyses.

9.2.1 Pharmacokinetic, Pharmacodynamic and Anti-drug Antibody Samples

Samples will be shipped to [redacted] for analysis either in house or at external laboratory. Study samples may be stored for a maximum of two years after completion of the study report.

9.3 Chain of Custody of Biological Samples

A full chain of custody is maintained for all samples throughout their life cycle.

The principal investigator keeps full traceability of collected biological samples from the patients while in storage at the centre until shipment and keeps documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed.

Sponsor keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

9.4 Withdrawal of Informed Consent for Donated Biological Samples

If a patient withdraws consent to the use of biological samples donated the samples will be disposed/destroyed, if not already analysed and documented.

The principal investigator:

- will ensure that patient withdrawal of informed consent is notified immediately to sponsor
- will ensure that biological samples from that patient, if stored at the study site, are immediately identified, disposed/destructed and the action documented.
- will ensure the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destructed and the action documented returned to the study site.

Sponsor ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destructed and the action documented returned to the study site.

In the event that analysis/research has already been performed, sponsor will retain the results and associated data for regulatory reasons but these will not be used in any subsequent analyses.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements.

10.2 Patient Data Protection

The informed consent form (ICF) will incorporate wording that complies with relevant data protection and privacy legislation.

10.3 Ethics and Regulatory Review

An ethical review board must approve the final study protocol, including the final version of the ICF and any other written information to be provided to the patients. The investigator will ensure the distribution of these documents to the applicable ethical review board, and to the study site staff. The opinion of the ethical review board must be given in writing.

Sponsor must approve any modifications to the ICF that are needed to meet local requirements.

Before enrolment of any patient into the study, the final study protocol, and the final version of the informed consent form are approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

The distribution of any of these documents to the national regulatory authorities will be handled by sponsor.

Sponsor will provide ethical review boards and principal investigators with safety updates/reports according to local requirements.

Progress reports and notifications of serious and unexpected adverse drug reactions will be provided to the ethical review board according to local regulations and guidelines.

10.4 Informed Consent

The principal investigator(s) at the centre will:

- Ensure that the patient is given full and adequate oral and written/read information about the nature, purpose, possible risk and benefit of the study.
- Ensure that the patients are notified that they are free to discontinue the study at any time.
- Ensure that the patient is given the opportunity to ask questions and allowed time to consider the information provided.
- Obtain and document the patient’s signed and dated informed consent before conducting any procedure specifically for the study.

- Ensure the original, signed informed consent form is stored in the Investigator's Study File.

- Ensure a copy of the signed informed consent form is given to the patient.

10.5 Changes to the Protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of the principal investigator and sponsor.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment.

The amendment must be approved by regulatory authorities and the ethical review board before implementation. Local requirements must be followed for amended protocols.

Sponsor will distribute any subsequent amendments and new versions of the protocol to the principal investigator.

If a protocol amendment requires a change to a centre's informed consent form, sponsor and the centre's ethical review board must approve the revised informed consent form before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by the ethical review board.

10.6 Audits and Inspections

The investigator(s)/institution will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.

Permission to examine, analyze, verify, and reproduce any records and reports that are important to evaluation of a clinical trial. Any party (e.g., domestic and foreign regulatory authorities, sponsor´s monitors and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirements(s) to maintain the confidentiality of subjects´ identities and sponsor´s proprietary information.

Authorised representatives of sponsor or a regulatory authority may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The investigator will contact sponsor immediately if contacted by a regulatory agency about an inspection at the centre.

11. STUDY MANAGEMENT

11.1 Pre-study Activities

Before the first patient is entered into the study, it is necessary for a representative of sponsor to visit the investigational study site for a pre-study visit to:

- Determine the adequacy of the facilities to give the sponsor information about whether the study centre has knowledge, enough time, a sufficient patient pool, and sufficient training to manage the study in a good way in terms of patient inclusion, patient handling, data and overall study management.

- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence and the responsibilities of sponsor or its representatives.

11.2 Training of Study Site Personnel

Before the first patient is entered into the study, a sponsor representative will review and discuss the requirements of the clinical study protocol and related documents with the investigational staff and also train them in any study specific procedures and system(s) utilised.

The principal investigator will ensure that appropriate training relevant to the study is given to all staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The principal investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

11.3 Monitoring of the Study

During the study, a sponsor representative will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s).

- Confirm that facilities remain acceptable.

- Confirm that the investigational team is adhering to the protocol, data are being accurately and timely recorded in the CRFs, and investigational product accountability checks are being performed.

- Perform source data verification (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will be done using print outs of records for each patient.

- Perform drug accountability.

- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed/destructed accordingly, and the action is documented, and reported to the patient.

The sponsor and the CRO will be available between visits if the investigator(s) or other staff at the centre needs information and advice about the study conduct.

11.4 Study Agreements

The principal investigator must comply with all the terms, conditions, and obligations of the clinical study agreement for this study. In the event of any inconsistency between this clinical study protocol and the clinical study agreement, the clinical study protocol will prevail.

Agreements between sponsor and the principal investigator must be in place before any study-related procedures can take place, or patients be enrolled.

11.5 Study Timetable and End of Study

The end of the entire study is defined as "the last visit of the last patient undergoing the trial".

The study is expected to start in Quarter 2 2016 and to be completed by Quarter 2 2017.

Sponsor may terminate the entire study prematurely if concerns for safety arise within the study.

11.6 Insurance

All patients in the study are covered by an insurance held by Hansa Medical AB.

12. DATA HANDLING

12.1 Source Data and Source Documents

12.1.1 Source Data and Source Documents

Source data – ICH Definition

Source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).

Source documents – ICH Definition

Source documents are defined as original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study).

12.2 Study specific Source Data Requirements – Hansa Medical AB

Any study specific source data will be described and defined in a Source Data document produced for this study.

12.3 Case Report Forms

A CRF/eCRF will be provided by a CRO. If an eCRF is chosen the system should be validated in accordance with regulatory and system requirements.

12.4 Data Management

All data management procedures will be outsourced to a CRO. Activities will be specified in a Data Management Plan prepared by the CRO and reviewed and approved by the Sponsor. The plan will be issued before data collection begins and will describe all functions, processes and specifications for data collection, cleaning and validation.

For medical coding of AEs, medical history and concomitant medication the most recent versions of the Medical Dictionary for Regulatory Activities (MedDRA) and WHO Drug will be used. The coding will be outsourced to a third party. When all data has been processed, queries resolved, medical coding completed and any issues from review of protocol violations and data listings resolved, the data base will be locked and any further update will be denied.

13. EVALUATION AND CALCULATION OF PHARMACOKINETIC AND PHARMACODYNAMIC VARIABLES

13.1 Calculation or Derivation of Pharmacokinetic Variables

IdeS concentration will be determined in collected PK samples and the result will be correlated with the achieved pharmacodynamic results. Only a limited pharmacokinetic evaluation will be performed. Where possible, the following PK parameters will be determined for IdeS: maximum plasma concentration (C_{max}) and area under the concentration-time curve (AUC_t).

13.2 Calculation or Derivation of the Relationship Between Pharmacokinetic and Pharmacodynamic Variables

Relationship between IdeS serum or plasma concentration and IgG and F(ab')$_2$ fragment concentrations (PD) as well as levels of ADAMTS13 activity and ADAMTS13 antibodies (IgG and F(ab')$_2$), respectively, will be presented graphically. If appropriate, concentration-effect relationships will be explored.

14. STATISTICAL METHODS AND SAMPLE SIZE

Prior to clean file a Statistical Analysis Plan (SAP) with details on statistical analysis and data presentation will be written. This will be outsourced to a CRO.

14.1 Description of Analysis Sets

The safety analysis set will consist of all subjects that received any amount of study medication.

The Full Analysis Set (FAS) will consist of all subjects in the safety set.

The Per Protocol Set (PPS) will be defined by the PK analyst.

The final criteria for the PPS, regarding which protocol deviations that warrant exclusions, will be determined when all data on protocol violations/deviations are available.

14.2 Methods of Statistical Analyses

14.2.1 General Principles

No formal statistical hypothesis testing will be performed in this study. Data will be presented by actual dose received.

14.2.2 Patient Characteristics

The following demographic variables will be tabulated: gender, race, date of birth, body weight, height and body mass index (BMI) for all patients as appropriate.

Medical history and medications taken before screening will be tabulated including comments and coded fields.

Baseline assessments of safety variables (ECG, vital signs, body temperature, physical examination, IgE and laboratory parameters) will be tabulated by dose groups as appropriate. Base line is defined as pre-dose assessments on treatment day 0.

14.2.3 Safety and Tolerability

All safety and tolerability data including safety labs, vital signs, weight, body temperature, ECG and physical exams will be tabulated as specified in the SAP.

Adverse events and serious adverse events will be collected for each patient from time when informed consent is obtained (visit 1) until end of study. AEs will be presented as pre-treatment emergent, treatment emergent and post-treatment emergent in separate listings.

The following summaries of AEs will be given by treatment and in total:

Severity, action taken, concomitant therapy started and subject outcome of the AEs will be given in data listings only. AEs with a fatal outcome and AEs which were reason for premature discontinuation of study drug will be listed separately, respectively.

The number of patients who had any AEs, SAEs, AEs that led to withdrawal, AEs related to study drug and AEs with severe intensity will be summarized. If the number of AEs are

sufficiently large summary will be broken down on PT (Preferred term) and SOC (System organ class) according to MedDRA vocabulary. Furthermore, SAEs and AEs that led to withdrawal will be tabulated separately.

14.2.4 Pharmacokinetics

Pharmacokinetic (PK) variables will be summarized using appropriate descriptive statistics (e.g., n, geometric mean, coefficient of variation (CV), min, median, max) by treatment group.

14.2.5 Pharmacodynamics

All data associated with the efficacy of IdeS in cleaving IgG (IgG and $F(ab')_2$ fragments concentrations) will be presented using listings for each dose group.

14.2.6 Anti-drug Antibodies

All anti-IdeS antibody data will be presented using listings for each dose group.

14.2.7 Efficacy

All data associated with the efficacy of IdeS; levels of ADAMTS13 activity, ADAMTS13 antibodies, [redacted], immunoglobulins (IgG, IgM and IgA) and [redacted] will be determined for each patient and presented in listings sorted by treatment, patient, and time-point. In addition, time for ADAMTS13 activity to return to normal levels and number of cases with normalisation of ADAMTS13 at 64 days will be presented per patient.

14.3 Determination of Sample Size

Sample size is not based on formal statistical considerations. Due to the exploratory nature of the study it is expected that data from six patients should suffice to achieve the objectives of the study.

15. REPORTING AND PUBLICATION

15.1 Clinical Study Report

The results from this study will be reported in a clinical study report (CSR) within one year after completion of the last patient. This will be prepared by Hansa Medical AB and submitted for comments and signature to the signatory investigator(s).

15.2 Confidentiality and Ownership of Data

Any confidential information relating to the IMP or the study, including any data and results from the study will be the exclusive property of Hansa Medical AB. The investigator and any other persons involved in the trial will protect the confidentiality of the proprietary information belonging to Hansa Medical AB.

15.3 Publication and Public Disclosure

15.3.1 Publication Policy

At the end of the study, one or more manuscripts for joint publication may be prepared in collaboration between the investigator(s) offered authorship and Hansa Medical AB.

Any external Contract Research Organisation or laboratory involved in the conduct of this study has no publication rights regarding the study.

15.3.2 Public Disclosure Policy

The study will be uploaded to the EudraCT database.

16. ARCHIVING

16.1 Investigator File

The investigator is responsible for maintaining all the records, which enable the conduct of the trial at the site to be fully understood, in compliance with ICH-GCP. The trial documentation including all the relevant correspondence should be kept by the investigator for at least 15 years after the completion or discontinuation of the trial, if no further instructions are given by Hansa Medical AB.

The investigator is responsible for the completion and maintenance of the confidential subject identification code, which provides the sole link between named subject source records and anonymous CRF data for Hansa Medical AB. The investigator must arrange for the retention of this Subject Identification Log and signed Informed Consent Documents for at least 15 years after the completion or discontinuation of the trial.

No trial site document may be destroyed without prior written agreement between the investigator and Hansa Medical AB. Should the investigator elect to assign the trial documents to another party, or move them to another location, Hansa Medical AB must be notified. If the investigator retires and the documents no longer can be archived by the site, Hansa Medical AB can arrange having the Investigator File archived at an external archive.

16.2 Trial Master File

Hansa Medical AB will archive the Trial Master File in accordance with ICH-GCP and applicable regulatory requirements.

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