An Open-Label Phase II study in anti-GBM disease (Goodpasture's disease) with Adverse Renal Prognosis to Evaluate the Efficacy and Safety of IdeS --GOOD-IDES

Study code: GOOD-IDES-01

Phase II study

STATISTICAL ANALYSIS PLAN

Signatures:

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Dec 16, 2020

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Dec 17, 2020

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Dec 18, 2020

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1 Abbreviations

AAV	ANCA-associated vasculitis
ADA	Anti-IdeS antibodies
AE	Adverse Event
ANCA	Anti-neutrophil cytoplasm antibody
ATC	Anatomical Therapeutic Chemical
AUC_{0-24}	Area under the concentration-time curve from time zero to 24 h
C_{max}	Maximum observed concentration
CL	Apparent total body clearance
CV	Coefficient of variation
eGFR	Estimated Glomerular Filtration Rate
FAS	Full Analysis Set
GBM	Glomerular Basement Membrane
IdeS	IgG-degrading enzyme of Streptococcus pyogenes, previous name of imlifidase
IgG	Immunoglobulin G
K_{21}	Transfer rate constant (first-order) from the peripheral (2) to central (1) compartment
MedDRA	Medical Dictionary for Regulatory Activities
PLEX	Plasma exchange
SAE	Serious Adverse Event
TAE	Treatment-emergent Adverse Event
t_{max}	Time to maximum observed concentration
$t_{1/2}$	Elimination half-life
V_{ss}	Steady-state volume of distribution
V_z	Volume of distribution during terminal phase
WhoDD	World Health Organization Drug Dictionary

2 Study objective(s)

The primary objective of this study is to evaluate the safety and tolerability of imlifidase (previously called IdeS) in patients with severe anti-GBM (Glomerular Basement Membrane) disease on background of standard care consisting of pulse-methylprednisolone, oral prednisolone and intravenous cyclophosphamide combined with plasma exchange (PLEX).

For efficacy, the primary objective is to evaluate the efficacy of an imlifidase based regimen to salvage independent renal function; defined as no need for dialysis at 6 months and after imlifidase treatment.

The secondary objectives are to assess the following:

- Renal function 3 months after imlifidase treatment
- Change in eGFR during the study period
- Number of days with anti-GBM antibodies above a toxic level (>20 U/ml)
- Disappearance of hematuria, days from start of treatment
- Change in proteinuria during the study measured as u-albumin/creatinine ratio in morning void
- Number of PLEX needed
- Changes in renal histology (optional)
- Anti-IdeS antibodies (ADA)
- Pharmacokinetics, Pharmacodynamics (IgG degradation)

3 Study endpoints

The primary efficacy endpoint is

- Proportion of subjects with independent renal function at 6 months after imlifidase treatment (defined as no need for dialysis at 6 months)

The secondary endpoints of this study include assessment of:

- The proportion of subjects with independent renal function, defined as no need for dialysis at 3 months after imlifidase treatment
- Renal function at 3 and 6 months expressed as eGFR and as change in GFR from baseline
- Number of days with anti-GBM antibodies above a toxic level (>20 U/ml) measured at a central laboratory using the Wieslab anti-GBM kit
- Disappearance of haematuria, measured in days from start of treatment
- Change in proteinuria during the study measured as u-albumin/creatinine ratio in morning void
- Number of PLEXs needed
- Renal histology measurements and changes in renal histology if a second renal biopsy is performed
- Anti-IdeS antibodies (ADA) levels
- Pharmacokinetics (AUC, C_{max}, t_{max}, $t_{1/2}$, CL, k_{21}, Vss, Vz), Pharmacodynamics (IgG degradation/change from baseline)

4 Design and type of the study

This is a pilot phase II, single-arm, open label, multicenter, multinational study of a single dose of imlifidase in patients with severe anti-GBM disease.

5 Sample size considerations

Since 1990, there are 11 case series published on anti-GBM disease with a total of 461 patients, the combined renal survival (patient alive and free from dialysis) among these historical controls at 6-12 months for patients with creatinine > 500 µmol/L was 7%. In a more recent not yet published study the renal survival was 20%. The present study also includes patients that are refractory to standard therapy, justifying the 7% figure to be used as historical control.

If imlifidase treatment would result in a renal survival rate similar to AAV (i.e. 50%) the study would have a power of 0.98 to detect a statistically significant difference versus historical control (7%) with a sample size of 15 (one-sided exact binomial test with a significance level of 5% (alfa)).

Based on the power calculations and recruitment feasibility it was decided to enrol 15 subjects in the study.

6 Statistical hypothesis

No formal statistical hypothesis testing will be conducted.

7 Analysis sets

Two analysis sets are planned, however if they are identical FAS will be the only analysis set presented.

7.1 Full Analysis Set (FAS)

The FAS will consist of all subjects enrolled in the study who have at least one efficacy measurement recorded (renal survival rate at 6 months or any of the endpoints listed for the secondary objective in Section 2). All efficacy analyses will be done for the FAS.

7.2 Safety Set

The safety set will comprise all subject who have received study treatment and will be used for all endpoints related to safety and tolerability.

8 General statistical considerations

All safety and efficacy data will be presented using descriptive statistics. Actual values and absolute change from baseline will be summarized by number of observations (n), arithmetic mean, median, standard deviation, minimum and maximum. Absolute change is defined as the observed difference between the values either positive or negative. Relative change will be summarized by number of observations (n), geometric mean, coefficient of variation (%), minimum and maximum. Categorical variables will be presented by counts and percentages. When relevant data will also be visually represented in graphs. All individual data will be presented in listings.

8.1 Handling of drop-outs or missing data

In general, missing values will not be substituted. However, partly missing dates will use the following imputation rules in calculations of durations (time since) (UNK indicates missing year, month, and day):

YYYY-MM-UNK: assume YYYY-MM-15

YYYY-UNK-UNK: assume date as YYYY-07-01

Negative durations will be set to 0.

If the entire date is missing (UNK-UNK-UNK) the date will be kept as missing and no duration will be derived.

In addition, for calculation of time to dialysis the following imputation will be done for all subjects:

UNK-MM-DD: if MM > Day 1 MM then YYYY= Day 1 YYYY, if MM ≤ Day 1 MM then YYYY=Day 1 YYYY+1

8.2 Examination of subgroups

All efficacy endpoints will be presented by the following two subgroups as well as for the total population:

- Dialys at baseline - defined as within 4 days before or the day after the imlifidase dose (i.e. dialysis reported at Day 3)
- Non-dialysis at baseline

9 Demographic and other baseline characteristics

Demography (age, gender, weight, height, heredity, smoking habits), premedication, co-morbidities and the following baseline characteristics will be summarized descriptively:

- Baseline Anti-GBM (U/ml), pre-dose Day 1
- Time since first renal symptom/sign (number of days from first renal symptom to Day 1)
- Time since first pulmonary symptom (number of days from first pulmonary symptom to Day 1)
- Time since first anti-GBM diagnosis (number of days from first anti-GBM diagnosis to Day 1)
- Time since first PLEX treatment for anti-GBM (number of days from first PLEX treatment for anti-GBM to Day 1)

10 Concomitant medication/treatment

Use of concomitant medication after study treatment (i.e. start date ≥ Day 1 or ongoing at Day 1) will be presented in a frequency table by ATC-code level 3 and preferred name (WhoDD).

11 Extent of exposure and compliance

Total dose imlifidase (mg) per subject will be presented descriptively.

12 Analysis of efficacy

12.1 Primary efficacy variable

The primary efficacy endpoint renal survival rate is defined as the proportion of subjects with no need for dialysis at 6 months (Visit 12 date), i.e. no dialysis event during 6 weeks preceding the visit, and will be presented with number of subjects and percentages. Deaths prior to visit 12 will be considered as an event (need for dialysis).

12.2 Secondary efficacy variables

Renal survival rate at 3 months

Renal survival rate at 3 months (renal function 3 months) is defined as the proportion of subjects with no need for dialysis at 3 months (Visit 10 date) defined as for the primary endpoint and will be presented with number of subjects and percentages. Deaths prior to visit 10 will be considered as an event (need for dialysis).

Change in eGFR

eGFR will be calculated using the MDRD equation for all subjects (without correction for ethnicity):

eGFR (ml/min/1.73m^2) = 186*(serum creatinine (µmol/L)/88.4$^{)-1.154}$*Age$^{-0.203}$*0.742[if female]

For subjects who died or are on dialysis eGFR will be set to 0 from the date of death/dialysis an onwards.

The endpoint will be the eGFR (ml/min/1.73m^2) as well as the relative change in eGFR (%) from baseline (Day 1 pre-dose) to 3 (Day 93, Visit 10) and 6 months (Day 180, Visit 12) respectively. eGFR will also be presented by category and time with the following categorization: 0-<30, 30-<60, 60 -<90 and >90.

Toxic anti-GBM

Anti-GBM antibodies, measured at Wieslab laboratories, above a toxic level (>20 U/ml) will be presented by visit in a frequency table. Anti-GBM levels will also be summarized descriptively and individual curves over time will be presented graphically with the toxic level included as reference.

Change in proteinuria

Relative change in proteinuria (u-albumin/creatinine ratio) (%) from baseline to each visit will be calculated and presented descriptively.

Number of PLEXs needed

Total number of PLEXs needed will be calculated as the sum before and after imlifidase administration for each subject and summarized descriptively

Renal histology measurements

Renal histology measurements (and changes in renal histology if a second renal biopsy is performed) will be listed only.

Anti-IdeS antibodies (ADA)

Anti-IdeS antibodies (ADA) levels will be summarized descriptively by visit.

Pharmacokinetics

Imlifidase concentration as well as AUC, C_{max}, t_{max}, $t_{1/2}$, CL, k_{21}, Vss, Vz will be presented descriptively including geometric mean and CV(%). Mean concentration-time curves and individual curves will be presented graphically. For $t_{1/2}$, the harmonic mean will be presented instead of the geometric mean and for t_{max}, only median, min and max will be presented. Serum concentrations below the quantifiable limit will be set to half the LLOQ in the plots with LLOQ indicated in the figure, and set to zero in summary calculations.

IgG degradation

IgG concentration (pharmacodynamics) and change from baseline to each visit will be listed and summarized descriptively.

SDS Page

SDS Page (0-5 points) will be listed and summarized by visit in a frequency table.

12.3 Additional analyses

Anti-neutrophil cytoplasm antibody (ANCA) levels will be listed and summarized descriptively by visit. Number of subjects double-positive for anti-GBM and ANCA (MPO-ANCA≥3.5 and/or PR3-ANCA≥2) will be summarized.

13 Analysis of safety and tolerability

13.1 Adverse events

All recorded adverse events (AEs) will be coded according to MedDRA system. AEs will be classified into treatment emergent (TAE) and post-treatment emergent AEs (>30 days after Day 1). Post-treatment emergent AEs will be presented in listings only. TAEs will be summarized by System Organ Class and preferred term and presented by relatedness. Serious adverse events (SAE) and AEs leading to withdrawal will be listed separately. Both number of subjects and number of events will be presented.

13.2 Laboratory safety variables

Actual values at each visit and change from baseline to end of study (last available measure) will be calculated for all laboratory parameters and presented descriptively. Values outside the normal reference ranges will be flagged in the subject listings.

13.3 Other safety variables

Vital signs will be summarized descriptively and change from normal to abnormal in physical examinations will be summarized in shift tables.

14 Completion and premature discontinuation

Subject disposition in terms of study completion and premature discontinuation will be listed together with the reason for discontinuation.

15 Deviations from the analyses planned in the study protocol

The primary comparison versus historical control will not be done using formal statistical analysis. The planned analyses of matched historical controls has been omitted as it was not considered feasible. Due to methodological problems with urine samples taken at clinics, time to disappearance of hematuria will not be presented.

16 Execution of statistical analyses

Statistical analyses will be performed by [redacted]

17 Hardware and software

Statistical analysis, tables and subject data listings will be performed with SAS® version 9.4 for Windows (SAS Institute Inc., Cary, NC, USA).

18 References

Clinical Study Protocol, Protocol Version 2.1 (21 December 2016; Sweden & Denmark) and Version 3.3 (13 February 2018; Austria, Czeck Republic & France).

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16.2.1.1 Subject disposition

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16.2.2.1 Protocol deviations

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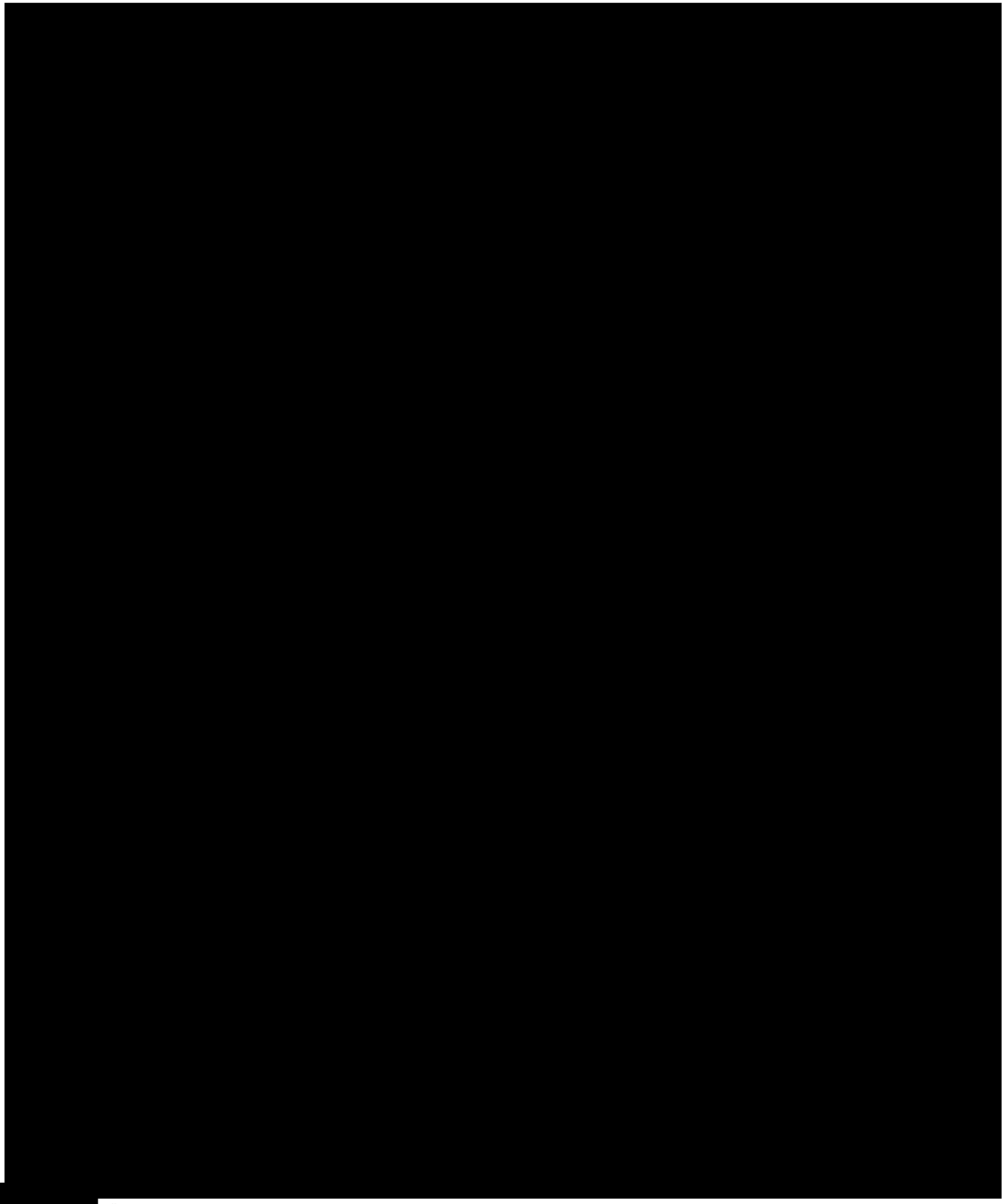

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