PCG Clinical Services

Statistical Analysis Plan

Study information

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Document history

Version	***Modified by (name and role)***	***Date***	***Description of Changes***
1.0	Malin Franzon, Senior Biostatistician	2018-12-13	Initial version
2.0	Malin Franzon, Senior Biostatistician	2019-01-22	Final version Updated after comments from the sponsor.

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1 Abbreviations

Abbreviation	*Explanation*
AE	Adverse Event
ALT	Alanine transferase
AST	Aspartate transferase
AUC	Area under the curve
BMI	Body mass index
CI	Confidence interval
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
DDP	Data display plan
DRM	Data Review Meeting
ECG	Electrocardiogram
FAS	Full analysis set
HBeAg	Hepatitis B envelope antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HDV	Hepatitis delta (D) virus
IAP	Interim Analysis Plan
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effects model for repeated measures
MXB	Myrcludex B
NTCP	Sodium taurocholate co-transporting polypeptide
PCR	Polymerase chain reaction
PEG-IFN alfa-2a	Peginterferon alfa-2a
PK	Pharmacokinetic
PKAS	Pharmacokinetic analysis set
PPAS	Per-protocol analysis set
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
T4	Thyroxine
TSH	Thyroid-stimulating hormone
ULN	Upper limit of Normal
WHO	World Health Organisation

2 Introduction

The Statistical Analysis Plan (SAP) is a complementary document to the Clinical Study Protocol and includes a more technical and detailed elaboration of the principal features of the proposed statistical analysis and presentations, and the way in which anticipated analysis problems will be handled.

If the SAP suggests changes to the principal features stated in the protocol, these should also be documented in a protocol amendment. Otherwise, it will suffice to record the changes in the SAP.

3 Study objectives

3.1 Primary objective

To investigate the efficacy of Myrcludex B in monotherapy and in combination with PEG-IFN alfa-2a and with Tenofovir compared to monotherapy with PEG-IFN alfa-2a, based on the achievement of undetectable viral load at the end of the follow-up period (6 months after the end of treatment).

3.1.1 Primary variables

The primary variable is the occurrence of (where proportions will be assessed):

- Negative PCR result of HDV RNA (HDV RNA negativation) at Week 72 (end of the follow up period).

3.2 Secondary objectives

- To investigate the efficacy of Myrcludex B in monotherapy and in combination with PEG-IFN alfa-2a and with Tenofovir as compared with monotherapy with PEG-IFN alfa-2a, based on the secondary efficacy endpoints;
- To investigate the safety of Myrcludex B in monotherapy and in combination with PEG-IFN alfa-2a and with Tenofovir compared with PEG-IFN alfa-2a monotherapy;
- To investigate the pharmacokinetics of Myrcludex B when administered in combination with PEG-IFN alfa-2a and with Tenofovir;
- To investigate the immunogenicity of Myrcludex B.

3.2.1 Secondary variables

The secondary variables are the occurrence of (where proportions will be assessed):

- Negative PCR result of HDV RNA (HDV RNA negativation) at Weeks 24 and 48;
- ALT normalization at Weeks 24, 48 and 72;
- Combined treatment response (negative PCR result of HDV RNA and ALT normalization) at Weeks 24, 48 and 72;
- HBsAg response HBsAg negativation or >1 log10 IU/mL decline) at Weeks 24, 48 and 72;
- HBsAg negativation with the appearance of anti-HBsAg antibodies at Weeks 48 and 72;
- HBsAg negativation without appearance of anti-HBsAg antibodies at Weeks 48 and 72;
- Negative PCR result of HBV DNA at Weeks 24, 48 and 72.

Additionally, the following secondary variables will be assessed:

- The intensity of liver fibrosis based on results of transient elastometry of liver at Weeks 48 and 72;
- Changes in the results of liver biopsy before and after the treatment as part of the study of efficacy;
- HBV, HDV genotyping, resistance assay and study of NTCP polymorphism.

3.2.2 Safety variables

The safety variables are:

- Adverse events, serious adverse events;
- Physical examination;
- Ophthalmological examination;
- Vital signs;
- 12-lead ECG;
- Haematology;
- Blood chemistry;
- Total bile acids;
- Coagulogram;
- Urinalysis;
- Blood test for TSH, T4.

3.2.3 Immunogenicity variables

The level of antibodies to Myrcludex B (arms B - F).

3.2.4 Pharmacokinetic variables

Plasma concentrations for Myrcludex B for main-study and sub-study (B-D) and sub-study (E-F).

Pharmacokinetic parameters for Myrcludex B for the sub-studies:

- C_{max} – maximum concentration;
- T_{max} – time of maximum concentration;
- K_{el} – elimination rate constant;
- $T_{1/2}$ – elimination half-life;
- CL/F – total clearance;
- AUC_{0-t} – area under the curve "drug concentration-time" from time 0 to the sampling time (t) of the last sample;
- $AUC_{0-\infty}$ – area under the curve "drug concentration-time" from time 0 to ∞.

PCG will receive the PK parameters to be included in descriptive analyses.

4 Study design

This study is a multicenter, open-label, randomized, comparative, parallel-arm phase II study.

It is planned that a total of 90 patients will be randomized using two separate randomisation lists in two phases of the study.

In Phase I, 60 patients will be randomized to the following groups:

- Arm A (n=15): PEG-IFN alfa-2a 180 µg during 48 weeks
- Arm B (n=15): Myrcludex B 2 mg + PEG-IFN alfa-2a 180 µg during 48 weeks
- Arm C (n=15): Myrcludex B 5 mg + PEG-IFN alfa-2a 180 µg during 48 weeks
- Arm D (n=15): Myrcludex B 2 mg during 48 weeks

In Phase II, 30 patients will be randomised to the following groups:

- Arm E (n=15): Myrcludex B 10 mg (10 mg once a day) + PEG-IFN alfa-2a 180 µg during 48 weeks
- Arm F (n=15): Myrcludex B 10 mg (5 mg twice a day) + Tenofovir during 48 weeks

All treatment groups will have a treatment period of 48 weeks with a follow-up period of 24 weeks after the treatment. Patients from group F will continue Tenofovir treatment during follow-up period.

The treatment arms are grouped into 2 phases:

Phase I – patients randomised to groups A – D

Phase II – patients randomised to groups E – F

It is planned to perform a pharmacokinetic study of Myrcludex B during the study:

1. Pharmacokinetic sub study (PK sub study)

   10 patients randomized to each of treatment arms B and C (20 patients in total) will be enrolled, where blood sample will be collected at Day 1, 2 and at Day 14, 15 (where the patients will be hospitalized during the collection).

2. Pharmacokinetic main study (PK main study)

   All patients of each MXB arm (Arm B, C, D, E and F) will be included.

   For the patients not participating in the pharmacokinetic sub study, a blood sampling point at a randomization visit (in 1hour +/-15 min after the drug injection) is assigned.

   Blood sample will be collected 1h±15min after injection at visits Week 4, 8, 12, 16, 20, 24, 28, 32 and 40 and at Week 48 for groups E and F only.

3. Pharmacokinetic study in group F (second part of study)

   10 patients of group F will take part, where blood samples will be collected at Day 1, 2 and Day 14, 15 (where the patients will be hospitalized during collection).

5 Study population

The study plans to randomize 90 male and female patients aged 18 through 65 years of age with chronic viral hepatitis B with delta-agent. To account for drop-outs during the randomization period, 123 patients are planned to be screened for the study.
The study selection criteria suggest the enrolment of patients with a positive result of HDV RNA, anti-HDV antibodies, HBeAg-positive or negative chronic hepatitis B, ALT level ≥ 1 ULN and <10 ULN, and with no co-infection with the hepatitis C virus or HIV.

5.1 Sample size

The primary endpoint (negative result of PCR on HDV RNA at Week 72) was used to justify the minimum size of treatment arms.
The calculation of the sample size was carried out according to the method described in the book by Chow Sh.-Ch., Sample Size Calculations in Clinical Research [Chow Sh.-Ch., Shao J., Wang H., 2008], by means of the TrialSize package for the R programming language.

The results of the previous MYR 201 substudy, data at the 24 treatment week were used: in Group of peginterferon therapy peginterferon alfa-2a 180 µg for 48 weeks, the proportion of participants with negative PCR result of HDV RNA was 29% (2 of 7 participants), in arm of combined therapy Myrcludex B 2 mg + peginterferon alfa-2a 180 µg for 24 weeks, followed by peginterferon alfa-2a 180 µg for 24 weeks, the proportion of participants with a negative PCR result of HDV RNA was 71% (5 of 7 participants).

It is expected that five clinical study groups will demonstrate efficacy comparable to combined therapy results in MYR 201 substudy. Under such assumptions and a given critical value of the significance level of 0.10, the group size n = 15 will make it possible to reach the power of a study more than 60%.

Considering the exploratory nature of the study, the calculated number of arms can be considered sufficient to obtain conclusions about the optimal dosing schedule to be used in clinical studies of the following phases.

6 Assessments

A schedule of assessments from the protocol is presented in Appendix A: Schedule of assessments.

6.1 Demographics and other baseline characteristic

Demographic data

- Date of birth;
- Sex;
- Race;
- Data on bad health habits: smoking, drinking and drug use, drug abuse.

Medical history

- Diagnosis/symptom;
- Degree of severity of the disease according to CTCAE;
- Start and end date;
- Information if the disease is resolved.

Previous and concomitant medication

- Drugs;
- Non-medicinal methods of treatment.

Body height and weight

- Body height (cm);
- Body weight (kg);
- BMI.

Urine pregnancy test

Urine drug screening

Alcohol-breath test

Alpha-fetoprotein blood test
Abdominal ultrasound

Serologic assay

- Anti-HIV antibodies;
- Anti-HCV antibodies and HCV RNA;
- Anti-HDV antibodies;
- Non-quantitative HBsAg analysis to assess the acceptability of the patient to participate in the study;
- Non-quantitative HBeAg analysis;
- Anti-HBsAg antibodies;
- Anti-HBeAg antibodies.

6.2 Efficacy assessments

Virology parameters:

- HDV RNA by a quantitative PCR method;
- HBsAg level by a quantitative EIA method;
- HBV DNA by a quantitative PCR method;
- Anti-HBsAg antibodies (only in patients with undetectable quantitative HBsAg).

Fibroscan (transient elastometry of the liver)

- To assess fibrosis.

The liver biopsy

ALT

6.3 Safety assessments

- Adverse events, serious adverse events;
- Physical examination;
- Ophthalmological examination;
- Vital signs;
- 12-lead ECG;
- Hematology;
- Blood chemistry;
- Coagulogram;
- Urinalysis;
- Total bile acids;
- Blood test for TSH, T4.

6.4 Pharmacokinetic assessments

6.4.1 Pharmacokinetics in sub study (PK sub-study)

Blood sample for estimation of drug concentration will be collected at Day 1, 2 and at Day 14, 15 at the following timepoints:

- Day 1 – before the first injection of Myrcludex B, in 00:30, 1:00, 1:30, 2:00, 2:30, 3:00, 4:00, 5:00, 6:00, 8:00, 10:00, 12:00, 14:00 (hh:min) after the drug injection;
- Day 2 – in 24:00 (hh:min) after the drug injection;
- Day 14 – before injection of Myrcludex B, in 00:30, 1:00, 1:30, 2:00, 2:30, 3:00, 4:00, 5:00, 6:00, 8:00, 10:00, 12:00, 14:00 (hh:min) after the drug injection;
- Day 15 – in 24:00 (hh:min) after the drug injection.

6.4.2 Pharmacokinetics in main study (PK main study)

Blood sampling points for the pharmacokinetic study are assigned: Week 4, 8, 12, 16, 20, 24, 28, 32, 40, 481 (in 1hour +/-15 min after the drug injection)

6.4.3 Pharmacokinetics in group F

Blood samples for estimation of drug concentration will be collected at Day 1, 2 and Day 14, 15 at the following timepoints:

- Day 1 – before the first injection of Myrcludex B, in 00:30, 1:00, 1:30, 2:00, 2:30, 3:00, 4:00, 5:00, 6:00, 8:00, 10:00, 12:00 (hh:min) after the drug injection;
- Day 2 – in 12:00 after the second injection in Day 1;
- Day 14 - before injection of Myrcludex B, in 00:30, 1:00, 1:30, 2:00, 2:30, 3:00, 4:00, 5:00, 6:00, 8:00, 10:00, 12:00 (hh:min);
- Day 15 - in 12:00 (hh:min) after the second injection in Day 14.

7 Method of analysis

7.1 General

All statistical analyses will be performed in accordance with the ICH E9 guideline for Statistical Principles for Clinical Trials (1), using SAS® (Version 9.4 or higher, SAS Institute Inc., Cary, NC, USA).

The groups B-D in Phase I will be compared with the control group A. Group A will also work as a control group for the Phase II of the study (2).

7.1.1 Presentation of results

All results will be presented by treatment group and in total, unless stated otherwise. It should be clearly stated which unit applies to each presented variable.

Continuous data will be summarised using descriptive statistics, and the following parameters will be reported:

- number of subjects with evaluable observations and missing observations;
- arithmetic mean and standard deviation;
- median;
- first and third quartiles;
- minimum and maximum.

Categorical data will be presented using absolute frequency and percentage. When the absolute frequency is zero, the percentage will not be presented. Unless stated otherwise, the denominator for percentage calculations will be the total number of subjects in the applicable analysis set, including subjects with missing data. For variables with missing values, the number and percentage of subjects with missing values will be presented.

Significance tests in this study will be two-sided and performed in the framework of explorative analysis. When reporting the results of significance tests, p-values will be presented.

All confidence intervals presented will be two-sided with a nominal confidence level of 95%.

Data will be presented using an appropriate number of decimal places, to ensure that undue precision is not implied (*e.g.* the number of decimals should not exceed the accuracy of the measuring instrument). Raw data will be presented with the same number of decimals as collected, and derived data with an appropriate number of decimals based on general practice, mathematical rationale or scientific rationale.

Minimum and maximum values will be presented with the same number of decimals as the analysed variable and the other descriptive statistics will be presented with one decimal more. Percentages and proportions will be presented with one decimal. Confidence interval bounds will be presented with the same number of decimals as the corresponding point estimate, and p-values will be presented with 4 decimals or as ‘<.0001’.

Mock tables and graphs are presented in the Data Display Plan (DDP), which is a supplementary document to this analysis plan. Individual subject data listings will be presented according to the ICH E3 guideline for Structure and Content of Clinical Study Reports (3), unless stated otherwise.

7.1.2 Baseline

Unless stated otherwise, the baseline value for a parameter is defined as the last non-missing value before the first dose of the study treatment.

7.1.3 Analysis relative day

The analysis relative day for an assessment/value is defined as the time in days from the date of randomisation to the date of the assessment. The date of randomisation is considered as day 1, and earlier dates will correspond to a negative day.

7.1.4 Analysis visit

An analysis visit is defined as a categorical variable used to classify values within an analysis variable into temporal or conceptual groups used for analyses.

The visits as defined in the case report form, CRF, will be used as analysis visits.

In general, data from unscheduled visits will be presented in data listings only and not included in analysis or summary tables. An exception to this is data used to confirm eligibility in association with screening or randomisation where the last assessment will be considered in summaries of screening data.

7.1.5 Handling of missing data

In general, no imputations of missing data will be performed, and the analyses will be performed on the observed cases, unless stated otherwise.

For all response variables, the missing equals failure (MEF) approach will be used for the main analysis (*i.e.*, subjects with missing data will be considered as non-responders).

Data listings will include the observed values. For derived variables, values based on imputed data can be presented in listings.

7.1.6 Interim analyses

The two parts Phase I and Phase II of the study will be finalised and analysed at separate time points.

- Final Phase I: When groups A-D have finished, final analysis will be performed for these groups;
- Final Phase II: When group E-F (which started after group A-D) have finished, final analyses for all groups (A-F) will be performed.

For Phase II (group E-F), there will be an interim after 24 weeks which will be described separately in an Interim Analysis Plan (IAP).

7.1.7 Multiplicity

Considering the explorative nature of this study no adjustment for multiple testing will be performed.

7.1.8 Subgroups

Analysis of ALT normalization will be repeated for subjects with abnormal ALT values at baseline.

7.2 Analysis sets

The decision on the classification of subjects to each analysis set will be taken at the data review meeting (DRM) and documented in the DRM report together with the reasons for excluding subjects from analysis sets.

7.2.1 Full analysis set

The full analysis set (FAS) is defined as all randomised subjects who received at least one dose of the study medication.

Analysis of the full analysis set will be based on the planned treatment (*i.e.* subjects will be analysed 'as randomised').

7.2.2 Per-protocol analysis set

The per-protocol analysis set (PPAS) is defined as the subset of subjects in the full analysis set for whom no protocol deviation judged as having an impact on the primary efficacy analysis was reported or identified.

The decision as to which protocol deviations should be considered as reason for exclusion from the per-protocol analysis set should be made at the DRM and documented in the DRM report.

Analysis on the per-protocol analysis set will be based on the actual treatment (*i.e.* subjects will be analysed 'as treated').

7.2.3 Safety analysis set

The safety analysis set is defined as all subjects who received at least one dose of the study medication.

Analysis on the safety analysis set will be based on the actual treatment (*i.e.* subjects will be analysed 'as treated').

7.2.4 Pharmacokinetic analysis set

Generally, the pharmacokinetic analysis set (PKAS) is defined as the subset of subjects in the safety analysis set for whom data on the blood drug concentration were obtained.

As there are separate PK studies involved, one PK analysis set will be formed for each PK study:

- PKAS – sub-study
  Subjects in the safety analysis set who also are included in the PK sub-study (group B and C)
- PKAS – main study
  Subjects in the safety analysis set who also are included in the PK main-study (any MXB group)
- PKAS – group F
  Subjects in the safety analysis set who also are included in the PK Group F sub-study

7.3 Disposition of subjects

The following will be presented:

- Number of screened subjects, in total;
- Number of screening failures, in total;
- Number of randomised subjects, by treatment group and in total.

Based on the number of randomised subjects, the following will also be presented, by treatment group and in total:

- Number and percentage of subjects who did not receive any dose of study medication;
- Number and percentage of subjects who received at least one dose of study medication;
- Number and percentage of subjects who completed the study;
- Number and percentage of subjects who withdrew prematurely from the study;
- Number and percentage of subjects in each of the analysis sets.

In addition, a frequency table on the primary reason for premature withdrawal from the study will be presented by treatment group and in total. Percentages for this table will be based on the number of prematurely withdrawn subjects.

The number of subjects attending each study visit will also be summarised.

7.4 Protocol deviations

The number and percentage of randomised subjects with at least one major protocol deviation leading to exclusion from an analysis set will be presented.

7.5 Demographics and baseline characteristics

Summary statistics and frequencies on demographic data will be presented for the Safety and FAS datasets.

The following variables will be summarised descriptively:

Demographic data:

- Demographics: Age, sex, and race;
- Data on bad health habits: smoking, drinking and drug use, drug abuse;
- Baseline anthropometrics: height, body weight, body mass index (BMI) and BMI categories ('<30 kg/m²' and '≥30 kg/m²').

Baseline data (collected at screening and/or randomisation visit):

- Urine drug test: amphetamine, barbiturates, benzodiazepine, cocaine, marijuana, methadone, opiates, tricyclic antidepressants;
- Alcohol breath test;
- Serum alpha fetoprotein (AFP) test [IU/mL];
- Abdominal ultrasound
- Serology test: anti-HIV antibodies, HCV RNA and anti-HCV antibodies, anti-HDV antibodies, HBsAg, HBeAg, anti-HBsAg antibodies, anti-HBeAg antibodies.

The arithmetic mean, standard deviation, medians and quartiles will be calculated for quantitative variables. The frequencies of the values and percentages will be calculated for dichotomous variables.

7.6 Medical history and concurrent diseases

Medical history and concurrent diseases will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA).

For each system organ class and preferred term, the number and percentage of subjects with at least one condition in that system organ class or preferred term will be presented. Medical history and concurrent diseases will be presented in separate tables, based on the safety analysis set.

Medical history is defined as events stopped prior to baseline. Concurrent diseases are defined as ongoing events and events stopped on or after baseline. If the start and/or stop date is partially unknown, the following imputation rules will be used for the purpose of classifying the events:

	Imputed start date	***Imputed end date***
Unknown year	Missing	Missing
Unknown month	1 January	31 December
Unknown day	First of month	Last of month

If it is not possible to classify the condition based on the reported and/or imputed start and end dates, it will be considered as concurrent. In data listings, the dates will be presented as reported.

7.7 Prior and concomitant medication

Medications will be coded according to the World Health Organisation (WHO) Drug Dictionary and summarised by therapeutic subgroup (ATC level 2) and preferred name.

For each therapeutic subgroup and preferred name, the number and percentage of subjects who used at least one medication of that therapeutic subgroup or preferred name will be presented. Prior and concomitant medications will be summarised in separate tables, based on the safety analysis set.

If a reported medication cannot be coded with a preferred name, the lowest available higher-level dictionary term will be used instead in the summary tables. If a medication cannot be coded on a lower level than the therapeutic subgroup or the anatomical main group (ATC level 1), that medication will be presented as 'Not codable' under that therapeutic subgroup/anatomical main group.

Prior medication is defined as medication stopped prior to baseline. Concomitant medication is defined as ongoing medication or medication stopped on or after baseline. If the start and/or stop date is partially unknown, the following imputation rules will be used for the purpose of classifying the medication:

	Imputed start date	***Imputed end date***
Unknown year	Missing	Missing
Unknown month	1 January	31 December
Unknown day	First of month	Last of month

If it is not possible to classify a medication based on the reported and/or imputed start and end dates, it will be considered as concomitant. In data listings, the dates will be presented as reported.

7.8 Efficacy evaluation

All analyses of efficacy variables will be performed on both the full analysis set (main analysis) and the per-protocol analysis set (supportive analysis).

For response variables, the missing equals failure (MEF) approach will be used as also described in paragraph 7.1.5 (handling of missing data).

In addition to the statistical hypothesis testing described in the subsections below, all efficacy variables will be summarised descriptively by treatment group and visit, for both the FAS analysis set and the per-protocol analysis set.

The arithmetic mean, a 95% confidence interval for the mean, standard deviation, medians and quartiles will be calculated for quantitative variables. The frequencies of the values, percentages, and 95% confidence intervals for the frequencies under the Clopper-Pearson method will be calculated for dichotomous variables.

7.8.1 Primary efficacy variable: HDV RNA response at Week 72

The proportions of negative HDV RNA response at Week 72 in each of the Myrcludex treatment groups (B-F) will be compared with the control group of Peginterferon alfa-2a by using Fisher's exact test and by presenting exact unconditional 95%-confidence intervals based on scores for the proportion differences.

The frequencies and proportions of participants with HDV RNA response at Week 72 will be presented by treatment group along with the p-values and confidence intervals for the comparison versus group A.

In addition to FAS using MEF approach for main analysis and PPAS as supportive, the following sensitivity analysis will be performed for the primary efficacy variable:

- FAS with observed cases (excluding missing values);

7.8.2 Secondary efficacy variables: proportions

The following secondary efficacy variables involving proportions will be analysed in the same way as for the primary efficacy variable. For each comparison Arm B-F versus Arm A, the hypotheses of equal proportions will be tested using Fisher's exact test and by presenting exact unconditional 95%-confidence intervals based on scores for the proportion differences.

- HDV RNA response at Week 24 and Week 48;
- ALT normalization at Weeks 24, 48 and 72;
- Combined response of negative HDV RNA and ALT normalization at Weeks 24, 48 and 72;
- HBsAg negativation with the appearance of anti-HBsAg antibodies at Weeks 48 and 72;
- HBsAg negativation without appearance of anti-HBsAg antibodies at Weeks 48 and 72;
- HBV DNA response at Weeks 24, 48 and 72;

7.8.3 Intensity of liver fibrosis

Summary statistics of Intensity of liver fibrosis at baseline (screening), Weeks 48 and 72 (as measured in kPa using transient elastometry/FibroScan) will be presented as well as change from baseline. Wilcoxon Mann-Witney test (also called Wilcoxon rank-sum test) will be used to compare change from baseline at week 48 and 72 between each of Arm B-F versus Arm A.

7.8.4 Change in liver biopsy result

The number and percentage of subjects with an improvement (decrease) or worsening (increase) of at least 1 point will be presented for the following parameters:

- Fibrosis:
  - Ishak fibrosis score
  - Knodell fibrosis score
  - METAVIR fibrosis stage
- Histological activity stage:
  - Histological activity index
  - METAVIR activity grade

Descriptive statistics for the following molecular analysis and gene expression parameters will be presented based on log-10 transformed data as well as non-transformed data, including the change from baseline for the transformed data:

- Molecular analysis:
  - Relative HDV RNA expression
  - relative HBV pregenomic expression
  - relative total HBV RNA expression (X region)
  - relative HBV RNA expression (S region)
  - total HBV DNA (X region) copies/cell
  - HBV DNA (S region) copies/cell
  - cccDNA copies/cell
  - HDAg positive Hepatocytes %

- Gene expression:
  - CXCL10 relative expression
  - NTCP relative expression
  - CYP7A1 relative expression
  - ISG15 relative expression

7.8.5 Other efficacy variables

HDV RNA levels and HBV DNA levels (on log-10 scale) will be analysed using mixed-effects model for repeated measures (MMRM) with time-point estimates. The MMRM analysis for HDV RNA will be used as a sensitivity analysis.

HDV RNA levels and HBV DNA levels (on log-10 scale) will also be presented descriptively. For Week 72 (follow-up visit), the change from Week 48 to Week 72 will be included as well.

Data will also be presented graphically, in line charts displaying the mean log-transformed levels over time.

HBV and HDV genotyping will be presented descriptively by visit.

7.9 Pharmacokinetic evaluation

All analyses and summaries of PK data will be based on the PK analysis set.

7.9.1 Pharmacokinetics in main study (PK main study)

For Myrcludex B plasma concentrations, summary statistics (including the geometric mean, and the arithmetic and geometric coefficients of variation [CV%]) will be presented by visit. Data will also be presented graphically, in line charts where the mean plasma concentration is plotted against time.

7.9.2 Pharmacokinetics in sub studies (group B-C and group F)

For plasma concentrations, summary statistics, including the geometric mean and arithmetic and geometric CV%, will be presented by visit and timepoint.

For the PK parameters, summary statistics (including the geometric mean, and the arithmetic and geometric coefficients of variation [CV%]) will be presented by Day (1, 2, 14 and 15).

7.10 Safety evaluation

All evaluations of safety data will be performed on the safety analysis set.

7.10.1 Extent of exposure

Exposure to Myrcludex B will be presented for each of the MXB groups (Arm B, C, D, E and F) separately and in total. Summary statistics will be presented for:

- treatment duration (weeks);
- total dose (mg);
- dose intensity (mg/week);
- compliance (%).

Exposure to PEG-IFN alfa-2a will be presented for each of the groups A, B, C and E separately and in total. Exposure to Tenofovir will be presented for group F. For PEG-IFN alfa-2a and Tenofovir exposure, summary statistics will be presented for:

- treatment duration (weeks);
- total dose (mg);
- compliance (%).

7.10.2 Adverse Events

Adverse events will be coded according to MedDRA.

An overview of all adverse events will be presented, including the number and percentage of subjects with at least one, and the total number, of the following:

- Adverse events;
- Serious adverse events;
- Adverse events leading to withdrawal of the study medication or dose reduction;
- Fatal adverse events;
- Adverse events, broken down by severity;
- Adverse events, broken down by causality assessment.

The incidence of adverse events will be presented by system organ class and preferred term. For each system organ class and preferred term, the total number of adverse events as well as the number and percentage of subjects with at least one adverse event in that system organ class or preferred term will be presented. The incidence of serious adverse events will be presented in the same way.

Separate tables for the incidence of adverse events broken down by severity and the incidence of adverse events broken down by causality assessment will also be presented by system organ class and preferred term.

There will also be tables on the most frequently reported adverse events, on system organ class level and on preferred term level. The decision on the frequency cut-off for these tables will be taken during the analysis of the adverse events data in consultation with the author of the clinical study report and could be influenced by factors such as the overall number of adverse events, study design, and the nature of the indication. The frequency cut-off should be mentioned in a table note.

7.10.3 Laboratory

For the purpose of summary tables on laboratory test results, any value reported as below the lower limit of quantification or as undetectable will be considered as missing, and any value reported as above the upper limit of quantification will be considered as being equal to the upper limit. In data listings, the reported value will be presented.

Summary statistics on the test results and change from baseline, and shift tables on the categorisation of values in relation to the normal range, will be presented by visit for the following parameters:

- **Haematology:** Haematocrit [%], haemoglobin [g/dL], red blood cells, reticulocytes [‰], platelets [10^9/L], leucocytes [10^9/L], White blood cell differentials for neutrophils, eosinophils, monocytes, basophils and lymphocytes, erythrocyte sedimentation rate (ESR);
- **Blood chemistry:** total protein [g/L], albumin [g/L], aminotransferase (ALT) [U/L], aspartate aminotransferase (AST) [U/L], gamma glutamyl transferase (GGT) [U/L], Lactate dehydrogenase (LDH) [U/L], pancreatic amylase [U/L], alkaline phosphatase [U/L], lipase [U/L], triglycerides [mmol/L], total bilirubin [umol/L], direct bilirubin [umol/L], total cholesterol [mmol/L], creatinine [umol/L], urea [mmol/L], glucose [mmol/L], potassium [mmol/L], sodium [mmol/L], calcium [mmol/L], chloride [mmol/L], phosphate [mmol/L], C-reactive protein [mg/L];
- **Blood bile acids:** total bile acids [umol/L];
- **Coagulogram:** Activated partial thromboplastin time [aPTT], Prothrombin time.

Blood test for TSH, T4

Urinalysis data will be presented in listings only.

7.10.4 Physical examination

For all body systems examined, frequency tables on the investigator's assessment will be presented by visit. For post-baseline visits, the shift from baseline will also be presented.

7.10.5 Vital signs

For vital signs parameters, summary statistics will be presented by visit. For post-baseline visits, summary statistics on the change from baseline will also be presented.

7.10.6 Electrocardiogram

A frequency table on the overall evaluation (assessment of normality) of electrocardiogram (ECG) will be presented by visit. For post-baseline visits, the shift from baseline will also be presented.

7.10.7 Immunogenicity

Summary statistics for the anti-MXB antibodies concentration values and change from baseline will be presented by visit for the groups receiving Myrcludex B (Arm B-F). The number and percentage of positive subjects will also be presented.

7.11 Changes to planned analysis

This SAP is based on protocol version 5.0 May 19, 2018 (Translated into English August 7, 2018).

A protocol amendment will be written, which imply that this SAP may need to be updated after approval.

The suggested changes are that there will two final analyses, one for Phase I and for Phase II (+Phase I) and one interim after 24 weeks for Phase II (group E-F).

8 Derived variables

8.1 General

8.1.1 Change from baseline

Change from baseline will be computed as the difference between a post-baseline value and the corresponding baseline value.

Percentage change from baseline will be computed as 100 times the change from baseline divided by the baseline value.

8.1.2 Durations

In general, the duration of a time period will be computed as the time in days from the start date to the end date plus 1 day. The duration in weeks is derived by division by 7 days/week.

8.2 Disposition of subjects

A screening failure is defined as a screened but not randomised subject.

8.3 Demographics and baseline characteristics

8.3.1 Age

Age will be computed as the integer part of the time in years between the date of birth and the date the written informed consent was signed, using the SAS function `yrdif()` with the basis parameter set to 'age'. For subjects for whom only the year of birth is collected, age will be computed as the difference between the year the informed consent was signed and the year of birth.

8.3.2 Body mass index

BMI will be computed as the body weight in kg divided by the squared height in metres.

8.4 Efficacy variables

8.4.1 HDV RNA response (primary efficacy variable)

HDV RNA response is defined as HDV negativation (*i.e.,* HDV RNA level of zero).

8.4.2 Combined response

Combined response is defined as fulfilment of both of the following two conditions simultaneously:

- Response, as defined in section 8.4.1;
- Normalisation of ALT (i.e., ALT value is within the normal range).

8.5 Safety variables

8.5.1 Exposure

The Myrcludex B treatment duration (in weeks) will be computed based on the dates of the first and last injections.

The cumulative dose of MXB (in mg) will be computed as the sum of all injected doses of MXB.

The MXB dose intensity (in mg/week) will be computed as the cumulative dose of MXB divided by the duration of exposure to MXB.

Compliance with MXB treatment (in %) will be computed as the ratio of the cumulative dose of MXB to the planned total dose of MXB (planned daily dose multiplied by 24×7 days) multiplied by 100.

The duration of exposure to tenofovir (in weeks) will be computed based on the first date of drug dispensation and the last date of drug return. If the date of last drug return has not been reported, the duration will be considered as missing.

The durations will be computed according to section 8.1.2.

8.5.2 Physical examination

The analysis parameters will be dichotomous variables categorising the examination results as 'Normal' or 'Abnormal' (findings not reported as normal). For examinations reported as not done, the analysis value will be missing.

8.5.3 Immunogenicity

A subject will be considered as positive at a post-baseline visit if there was >2-fold increase in the concentration of antibodies compared to baseline (*i.e.*, if the ratio to baseline was > 2).

9 References

1. **ICH Harmonised Tripartite Guideline for Statistical Principles for Clinical Trials E9. February 1998.**

2. ICH Harmonised Tripartite Guideline for choice of control group and related issues in clinical trials E10. 2000.

3. ICH Harmonised Tripartite Guideline for Structure and Content of Clinical Trial Reports E3. November 1995.

4. Guideline on missing data in confirmatory trials. EMA; Committee for Medicinal Products for Human Use. 2010.

5. Clinical Study Protocol MYR 203, version 5.0 May 19, 2018 (translated into English August 7, 2018).

10 Signoff

We have read this SAP for the MYR 203 study and confirm that, to the best of our knowledge, the statistical analyses to be performed in this study are accurately described.

Hepatera LLC: Yana Deloveri, CEO

SIGNATURE AND DATE

Klaus Junge, External Biostatistician

SIGNATURE AND DATE

LINK Medical Research SAP Author: Malin Franzon, Senior Biostatistician

SIGNATURE AND DATE

Appendix A: Schedule of assessments

Table 1 Flow Chart

Procedures	SCR	Treatment period												Follow-up period				
Visits		1	2	3	4	5	6	7	8	9	10	11	12	13/EOT	FU1	FU2	FU3	FU4	FU5/EOF
Week (W)	W-4 -1	W 0	W 1	W 2	W 4	W 8	W 12	W1 6	W2 0	W2 4	W2 8	W3 2	W4 0	W48	EOT+ W2	EOT+ W4	EOT+ W8	EOT+ W12	EOT+ W24
Day	–28 - 1	1	8± 2	15 ±2	29 ±2	57 ±2	85 ±2	113 ±2	141 ±2	169 ±2	197 ±2	225 ±2	281 ±2	337+2	351±3	365±3	393±3	421±3	505±3
Informed consent	X																		
Demography, medical history	X																		
Physical examination	X						X			X				X					X
Body height, weight, BMI[2]	X						X			X				X					X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test	X									X				X					
Urine drug screening	X																		
Alcohol-breath test	X																		
Alpha-fetoprotein blood test	X																		
Blood test for HIV (HIV antibodies)	X																		
Blood test for Hepatitis C (anti-HCV antibodies, HCV RNA)[3]	X																		
Inclusion/Exclusion criteria	X																		
Randomization[4]	X	X																	
Anti-HDV antibodies	X																		
HBeAg, anti-HBeAg antibodies[5]	X									X				X					X

[2] Body height, weight, BMI are measured at screening; only weight is evaluated in the course of the study.
[3] Evaluation of HCV RNA is performed only if there is a positive result of anti-HCV antibodies.
[4] Randomization should be performed after confirmation of patient's eligibility according to inclusion/exclusion criteria within Day-3 – Day -1 of the study

Procedures	SCR	Treatment period													Follow-up period				
Visits		1	2	3	4	5	6	7	8	9	10	11	12	13/EOT	FU1	FU2	FU3	FU4	FU5/EOF
Week (W)	W-4 -1	W 0	W 1	W 2	W 4	W 8	W 12	W1 6	W2 0	W2 4	W2 8	W3 2	W4 0	W48	EOT+ W2	EOT+ W4	EOT+ W8	EOT+ W12	EOT+ W24
Day	–28 - 1	1	8± 2	15 ±2	29 ±2	57 ±2	85 ±2	113 ±2	141 ±2	169 ±2	197 ±2	225 ±2	281 ±2	337+2	351±3	365±3	393±3	421±3	505±3
HBsAg quantification	X[6]																		
Anti-HBsAg antibodies	X[7]													X[8]					X[9]
HDV RNA[10]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HBV DNA (quantification)		X		X	X		X			X		X		X				X	X
HBsAg (quantification)		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulogram	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood bile acids		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood test for TSH, T4	X						X			X				X					
Urinalysis	X	X			X	X	X	X	X	X	X	X	X	X					X
ECG	X						X			X				X					X
Abdominal ultrasound	X													X					X
Transient elastometry (Fibroscan)	X													X					X
Liver biopsy	X													X[11]					X[12]
Evaluation of immunogenicity		X					X			X				X		X		X	X
HBV, HDV genotyping		X																	

[6] Local laboratory, to confirm participation in the study
[7] Local laboratory, to confirm participation in the study
[8] At the end of the study, the determination of anti-HBsAg antibodies will be performed in a central virology laboratory using the appropriate archival samples (for the HBsAg determination) in those patients for whom a negative result of the HBsAg quantification was obtained at Visit 48.
[9] At the end of the study, the determination of anti-HBsAg antibodies will be performed in a central virology laboratory using appropriate archival samples (for HBsAg determination) in those patients for whom a negative result of the HBsAg quantification was obtained at Visit 72.
[10] On screening – a blood sample at room temperature, later – frozen blood samples.
[11] It shall be performed within ± 7 days from the date of the visit, only for groups D and F
[12] Should be performed only for groups A, B, C, E within ± 7 days from the date of the visit

Procedures	SCR	Treatment period													Follow-up period				
Visits		1	2	3	4	5	6	7	8	9	10	11	12	13/EOT	FU1	FU2	FU3	FU4	FU5/EOF
Week (W)	W-4 -1	W 0	W 1	W 2	W 4	W 8	W 12	W1 6	W2 0	W2 4	W2 8	W3 2	W4 0	W48	EOT+ W2	EOT+ W4	EOT+ W8	EOT+ W12	EOT+ W24
Day	–28 - 1	1	8± 2	15 ±2	29 ±2	57 ±2	85 ±2	113 ±2	141 ±2	169 ±2	197 ±2	225 ±2	281 ±2	337+2	351±3	365±3	393±3	421±3	505±3
NTCP polymorphism (frozen blood clot)		X																	
Resistance assay (frozen samples)		X												X[13]					
Drug dispensing		X			X	X	X	X	X	X	X	X	X	T[14]	T	T	T	T	
Filling the patient diary in		X	X	X	X	X	X	X	X	X	X	X	X	X	T[15]	T	T	T	T
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant treatment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetic main study (PK-main study, for patients in arms B - F)		X			X	X	X	X	X	X	X	X	X	X[16]					
Pharmacokinetic substudy (PK-substudy), for 10 patients from group B and 10 patients from group C		Days 1, 2, 14, 15 (hospitalization to the study center)[17]																	
Pharmacokinetic study for group F		Days 1, 2, 14, 15 (hospitalization to the study center)[18]																	

[13] In case of a patient's drop out of the study before the end of the treatment period, a resistance analysis is performed during the Premature Dropout Visit.
[14] "T" means Tenofovir dispensing during follow-up period
[15] "T" means filling the data into Patient's diary regarding Tenofovir in the follow-up period
[16] Only for patients from groups E - F
[17] Patients from groups B, C and F participated in the PK sub-study are not allowed to deviate in the schedule of visits in Day 1 and 2. Sample collection for PK analysis should be performed before and after th first injection of Myrcludex B. Thje second part of PK sub-study could be performed within ±1 day (Days 15 – 16)
[18] Patients from groups B, C and F participated in the PK sub-study are not allowed to deviate in the schedule of visits in Day 1 and 2. Sample collection for PK analysis should be performed before and after th first injection of Myrcludex B. Thje second part of PK sub-study could be performed within ±1 day (Days 15 – 16)

Procedures	SCR	Treatment period												Follow-up period				
Visits		1	2	3	4	5	6	7	8	9	10	11	12	13/EOT	FU1	FU2	FU3	FU4	FU5/EOF
Week (W)	W-4 -1	W 0	W 1	W 2	W 4	W 8	W 12	W1 6	W2 0	W2 4	W2 8	W3 2	W4 0	W48	EOT+ W2	EOT+ W4	EOT+ W8	EOT+ W12	EOT+ W24
Day	–28 - 1	1	8± 2	15 ±2	29 ±2	57 ±2	85 ±2	113 ±2	141 ±2	169 ±2	197 ±2	225 ±2	281 ±2	337+2	351±3	365±3	393±3	421±3	505±3
Ophthalmological examination[19]	X	*If there are any indications for the examination*																	

SCR: screening; W: week; FU: follow up; EOT: End of treatment; EOF: End of follow up, BMI: body mass index, EKG: electrocardiography, TSH: thyroid-stimulating hormone, T4: thyroxine

10 Signoff

We have read this SAP for the MYR 203 study and confirm that, to the best of our knowledge, the statistical analyses to be performed in this study are accurately described.

Hepatera LLC: Yana Deloveri, CEO

22.01.2019

Klaus Junge, External Biostatistician

22.01.2019

LINK Medical Research SAP Author: Malin Franzon, Senior Biostatistician

25.01.2019

Amendment to Statistical Analysis Plan

Study information

Sponsor study code:	MYR 203
Study title:	A Multicenter, Open-label, Randomized, Comparative, parallel-arm phase II study to Assess efficacy and safety of Myrcludex B in combination with Peginterferon alfa-2a versus Peginterferon alfa-2a alone in patients with chronic viral hepatitis B with delta-agent
Protocol version and date:	Amended protocol version 6.0 dated January 21, 2019
PCG study ID:	MYR003

Document control

Document Name	Statistical Analysis Plan Amendment
Version	1.0
Status	final
Author	Malin Franzon LINK Medical Research Kungsängsvägen 19 SE-753 23 Uppsala, Sweden e-mail: Malin.Franzon@linkmedical.se phone: +46 18 430 31 00 mobile: +46 73 142 11 89

Document history

Version	***Modified by (name and role)***	***Date***	***Description of Changes***
1.0	Malin Franzon, Senior Biostatistician	2019-05-17	Final version

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1 Purpose

The purpose of this amendment to the statistical analysis plan (SAP) is to describe changes to the final SAP version 2.0 after amendment protocol 6.0. Furthermore, handling of randomisation issues is also mentioned.

2 Handling of randomisation issues

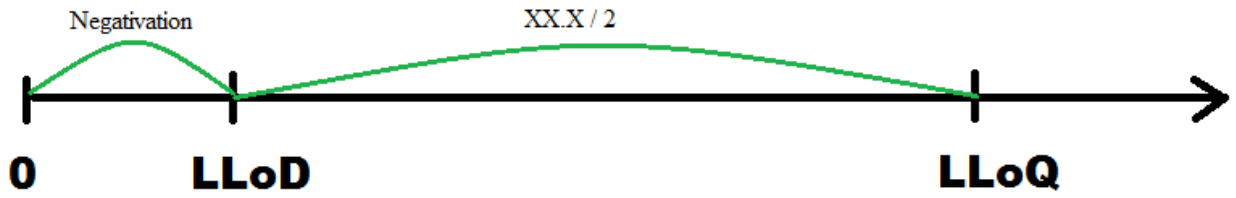
There are uncertainties regarding how randomisation has been performed in this study. This will be considered when interpreting the results in the clinical study report.

3 Amendment to sections in SAP

3.1 Handling of missing data and non-quantifiable values

Handling of missing data described in section 7.1.5 of final SAP v2.0 is amended to handle values below LLOD and LLOQ in the same way as study MYR202.

For the virology results and other parameters using LLOQ and/or LLOD values, the following rules will be applied:



- Values below the limit of detection (LLOD) will be imputed as zero values.
- Values reported as '<x' (below the lower limit of quantification, LLOQ), will be imputed as half the LLOQ value.
- 'Non-measurable' data will be considered as missing data.
- Values reported as '>x' (above the upper limit of quantification, ULOQ), will be imputed as the ULOQ value.

For the log-10 transformed data, missing values due to untransformed values of zero will be imputed as zero.

3.2 Interim analyses

Planned interim analyses were described in section 7.1.6 of final SAP v2.0. Below is a clarification of the interim analyses in accordance with amended protocol v 6.0.

There will be two interims in the study before the final analysis of all treatment arms.

1) Phase I: When groups A-D have finished, final analysis will be performed for these groups;
2) 24 weeks interim for Phase II (groups E-F).

The 24 weeks interim analysis for groups E-F in Phase II of the study (number 2) above) will be described separately in an Interim Analysis Plan (IAP).

3.3 Secondary efficacy variables: proportions

Section 7.8.2 of the final SAP v2.0 is amended to include the following the following secondary variable:

- HBsAg response (HBsAg negativation or >1 log10 IU/mL decline) at Weeks 24, 48 and 72.

The variable is included in section 3.2.1 of the final SAP v2.0, but not in section 7.8.2.

Analysis of this variable will be performed in the same way as for the other variables as described in section 7.8.2 of the final SAP v2.0.

3.4 Biopsy results

The following molecular analysis and gene expression parameters will be added to the list of parameters in section 7.8.4 of the final SAP v2.0:

- Molecular analysis:
  - HBsAg (from biopsy)

- Gene expression:
  - MX1 relative expression
  - OAS relative expression
  - HLA-E relative expression
  - TAP1 relative expression
  - USP18 relative expression

Furthermore, RNA content and DNA content (molecular analysis) will be listed.

3.5 Laboratory

The following amendments will be applied to section 7.10.3 of final SAP v2.0:

Missing data for laboratory will be handled as described in section 3.1 above.

For Haematology, summary statistics will be presented by visit for the following parameters:

- **Haematology:** leukocytes [10^9/L] with absolute [10^9/L] and relative [%] differentials: basophils, eosinophils, lymphocytes, monocytes, neutrophils; erythrocyte sedimentation rate (mm/h), haematocrit [%], haemoglobin [g/dL], platelets [10^9/L], red blood cells, reticulocytes (absolute10^9/L and relative ‰);

3.6 HDV RNA response

In section 8.4.1 of final SAP v2.0, HDV RNA response is defined as “HDV negativation (*i.e.,* HDV RNA level of zero)”. However, as described in section 3.1 above values below the limit of detection (LLOD) will be imputed as zero values. Hence, HDV negativation is defined as HDV RNA level of zero or below the limit of detection (LLOD).

3.7 Exposure to MXB and PEG-IFN

The following amendments will be applied to section 8.5.1 of final SAP v2.0:

Compliance with MXB treatment (in %) will be computed as the ratio of the cumulative dose of MXB to the planned total dose of MXB, where planned total dose of MXB will be calculated as planned daily dose multiplied by 48×7 days multiplied by 100 (as MXB is administrated daily for 48 weeks).

Compliance with PEG-IFN treatment (in %) will be computed as the ratio of the cumulative dose of PEG-IFN to the planned total dose of PEG-IFN, where planned total dose of PEG-IFN will be calculated as planned daily dose multiplied by 48 multiplied by 100 (as PEG-IFN is administrated once a week for 48 weeks).

4 Presentation of results

The updated version of the DDP Final 3.0 incorporates the changes described in this SAP amendment.

5 Signoff

We have read this SAP Amendment for the MYR 203 study and confirm that, to the best of our knowledge, the statistical analyses to be performed in this study are accurately described.

Hepatera LLC: Yana Deloveri, CEO

SIGNATURE AND DATE

Klaus Junge, External Biostatistician

SIGNATURE AND DATE

LINK Medical Research SAP Author: Malin Franzon, Senior Biostatistician

SIGNATURE AND DATE

3.7 *Exposure to MXB and PEG-IFN*

The following amendments will be applied to section 8.5.1 of final SAP v2.0:

Compliance with MXB treatment (in %) will be computed as the ratio of the cumulative dose of MXB to the planned total dose of MXB, where planned total dose of MXB will be calculated as planned daily dose multiplied by 48×7 days multiplied by 100 (as MXB is administrated daily for 48 weeks).

Compliance with PEG-IFN treatment (in %) will be computed as the ratio of the cumulative dose of PEG-IFN to the planned total dose of PEG-IFN, where planned total dose of PEG-IFN will be calculated as planned daily dose multiplied by 48 multiplied by 100 (as PEG-IFN is administrated once a week for 48 weeks).

4 Presentation of results

The updated version of the DDP Final 3.0 incorporates the changes described in this SAP amendment.

5 Signoff

We have read this SAP Amendment for the MYR 203 study and confirm that, to the best of our knowledge, the statistical analyses to be performed in this study are accurately described.

Hepatera LLC: Yana Deloveri, CEO

21.05.2019

Klaus Junge, External Biostatistician

21.05.2019

LINK Medical Research SAP Author: Malin Franzon, Senior Biostatistician

22.05.2019

Amendment 2 to Statistical Analysis Plan

Study information

Sponsor study code:	MYR 203
Study title:	A Multicenter, Open-label, Randomized, Comparative, parallel-arm phase II study to Assess efficacy and safety of Myrcludex B in combination with Peginterferon alfa-2a versus Peginterferon alfa-2a alone in patients with chronic viral hepatitis B with delta-agent
Protocol version and date:	Amended protocol version 6.0 dated January 21, 2019
PCG study ID:	MYR003

Document control

Document Name	Statistical Analysis Plan Amendment 2
Version	1.0
Status	final
Author	Malin Franzon LINK Medical Research Kungsängsvägen 19 SE-753 23 Uppsala, Sweden e-mail: Malin.Franzon@linkmedical.se phone: +46 18 430 31 00 mobile: +46 73 142 11 89

Document history

Version	***Modified by (name and role)***	***Date***	***Description of Changes***
0.1	Malin Franzon, Senior Biostatistician	2019-08-06	Initial version
1.0	Malin Franzon, Senior Biostatistician	2019-08-13	Final version. Updates with comments from sponsor.

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1 Purpose

The purpose of this amendment to the statistical analysis plan (SAP) is to describe changes to the final SAP version 2.0 and the first SAP Amendment dated 2019-05-17.

The rules for handling parameters using LLOD was stated in the first SAP Amendment, where values below the limit of detection (LLOD) will be imputed as zero values.

According to the first SAP Amendment: for the log-10 transformed data, log10(0) was then to be imputed as zero.

However, when LLOD<1 this may result in log10(<LLOD) being greater log(>LLOD) when log(>LLOD) is negative and log10(<LLOD) is imputed as zero.

This SAP Amendment 2 is a description of the correction of this, by imputing log(0) with log(LLOD/2) when LLOD<1.

This SAP Amendment 2 also describes adding of variables for post hoc analyses.

2 Amendment to SAP and first SAP Amendment

2.1 Handling of missing data and non-quantifiable values

Values below the limit of detection (<LLOD) will still be imputed as zero values, as described in the first SAP Amendment.

However, for the log-10 transformed data, the imputation is amended to the following:

- For the log-10 transformed data for parameters using LLOD values where LLOD>1, missing values due to untransformed values of zero will be imputed as 0
- For the log-10 transformed data for parameters using LLOD values where LLOD<1, missing values due to untransformed values of zero will be imputed as log10(LLOD/2).

2.2 Post hoc variables

The following the following post hoc variables will be added:

- Adjusted HDV RNA response: (>2log10 HDV RNA reduction or HDV RNA negativation) at Weeks 24, 48 and 72
- Adjusted combined response: ((>2log10 HDV RNA reduction or HDV RNA negativation) and ALT normalisation) at Weeks 24, 48 and 72

Analysis of these variables will be performed in the same way as for the other variables as described in section 7.8.2 of the final SAP v2.0. Mock tables are included in paragraph 3 below.

3 Presentation of results

The results will be presented in accordance with DDP Final 3.0 but with the following tables added for the Post hoc variables.

14.2.12 Post hoc analyses

14.2.12.1 Adjusted HDV RNA response: (>2log10 HDV RNA reduction or HDV RNA negativation) at Week 24, 48 and 72

Table 14.2.12.1-1. Adjusted HDV RNA response (>2 log10 HDV RNA reduction or HDV RNA negativation) at Week 24, 48 and 72. Statistical analysis of difference in proportions, using Fisher's exact test. Full analysis set

Table 14.2.12.1-2. Adjusted HDV RNA response (>2 log10 HDV RNA reduction or HDV RNA negativation) at Week 24, 48 and 72. Statistical analysis of difference in proportions, using Fisher's exact test. Per protocol analysis set

Adjusted HDV RNA response	PEG-IFN (N=xx)	MXB 2mg + PEG–IFN (N=xx)	MXB 5mg + PEG-IFN (N=xx)	MXB 2mg (N=xx)	MXB 10mg + PEG-IFN (N=xx)	MXB 5mg bid + Tenofovir (N=xx)
Week 24						
Number of subjects included in analysis	xx	xx	xx	xx	xx	xx
Proportion Response (95% CI)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x(xx.x, xx.x)
Difference in proportions (95% CI)		xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
p-value		0.xxxx	0.xxxx	0.xxxx	0.xxxx	0.xxxx
Week 48						
Number of subjects included in analysis	xx	xx	xx	xx	xx	xx
Proportion Response (95% CI)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x(xx.x, xx.x)
Difference in proportions (95% CI)		xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
p-value		0.xxxx	0.xxxx	0.xxxx	0.xxxx	0.xxxx
Week 72						
Number of subjects included in analysis	xx	xx	xx	xx	xx	xx
Proportion Response (95% CI)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x(xx.x, xx.x)
Difference in proportions (95% CI)		xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
p-value		0.xxxx	0.xxxx	0.xxxx	0.xxxx	0.xxxx

CI = Confidence interval, calculated using Clopper–Pearson (exact) for within group proportions and exact unconditional for difference in proportions.
Fisher's exact tests were used for the comparison of respective MXB group and PEG-IFN alfa-2 only group.
Source: <program name>.sas Date and time program was run: YYYY-MM-DDTHH:MM. Date and time analysis database was run: YYYY-MM-DDTHH:MM

For final Phase I, the table will only include the groups: "PEG-IFN", "MXB 2mg + PEG-IFN", "MXB 5mg + PEG-IFN", "MXB 2mg".

Table 14.2.12.1-3. Frequency table for Adjusted HDV RNA response (>2 log10 HDV RNA reduction or HDV RNA negativation) at Week 24, 48 and 72. Full analysis set

Table 14.2.12.1-4. Frequency table for Adjusted HDV RNA response (>2 log10 HDV RNA reduction or HDV RNA negativation) at Week 24, 48 and 72. Per protocol analysis set

Adjusted HDV RNA response	PEG-IFN (N=xx)	MXB 2mg + PEG−IFN (N=xx)	MXB 5mg + PEG-IFN (N=xx)	MXB 2mg (N=xx)	MXB 10mg + PEG-IFN (N=xx)	MXB 5mg bid + Tenofovir (N=xx)
Week 24						
Responder	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Non-responder	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Missing	xx	xx	xx	xx	xx	xx
Week 48						
Responder	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Non-responder	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Missing	xx	xx	xx	xx	xx	xx
Week 72						
Responder	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Non-responder	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Missing	xx	xx	xx	xx	xx	xx

Percentages are based on the number of subjects within each treatment group.
Source: <program name>.sas Date and time program was run: YYYY-MM-DDTHH:MM. Date and time analysis database was run: YYYY-MM-DDTHH:MM

For final Phase I, the table will only include the groups: "PEG-IFN", "MXB 2mg + PEG-IFN", "MXB 5mg + PEG-IFN", "MXB 2mg".

14.2.12.2 Adjusted combined response: ((>2log10 HDV RNA reduction or HDV RNA negativation) and ALT normalisation) at Week 24, 48 and 72

Table 14.2.12.2-1. Adjusted combined response ((>2 log10 HDV RNA reduction or HDV RNA negativation) and ALT normalisation) at Week 24, 48 and 72. Statistical analysis of difference in proportions, using Fisher's exact test. Full analysis set

Table 14.2.12.2-2. Adjusted combined response ((>2 log10 HDV RNA reduction or HDV RNA negativation) and ALT normalisation) at Week 24, 48 and 72. Statistical analysis of difference in proportions, using Fisher's exact test. Per protocol analysis set

Same as Table 14.2.12.1-1

Table 14.2.12.2-3. Frequency table for Adjusted combined response ((>2 log10 HDV RNA reduction or HDV RNA negativation) and ALT normalisation) at Week 24, 48 and 72. Full analysis set

Table 14.2.12.2-4. Frequency table for Adjusted combined response ((>2 log10 HDV RNA reduction or HDV RNA negativation) and ALT normalisation) at Week 24, 48 and 72. Per protocol analysis set

Same as Table 14.2.12.1-3

4 Signoff

We have read this SAP Amendment 2 for the MYR 203 study and confirm that, to the best of our knowledge, the statistical analyses to be performed in this study are accurately described.

Hepatera LLC: Yana Deloveri, CEO

SIGNATURE AND DATE

Klaus Junge, External Biostatistician

SIGNATURE AND DATE

LINK Medical Research SAP Author: Malin Franzon, Senior Biostatistician

SIGNATURE AND DATE

4 Signoff

We have read this SAP Amendment 2 for the MYR 203 study and confirm that, to the best of our knowledge, the statistical analyses to be performed in this study are accurately described.

Hepatera LLC: Yana Deloveri, CEO

SIGNATURE AND DATE

13.08.2019

Klaus Junge, External Biostatistician

SIGNATURE AND DATE

13.08.2019

LINK Medical Research SAP Author: Malin Franzon, Senior Biostatistician

SIGNATURE AND DATE

Amendment 3 to Statistical Analysis Plan

Study information

Sponsor study code:	MYR 203
Study title:	A Multicenter, Open-label, Randomized, Comparative, parallel-arm phase II study to Assess efficacy and safety of Myrcludex B in combination with Peginterferon alfa-2a versus Peginterferon alfa-2a alone in patients with chronic viral hepatitis B with delta-agent
Protocol version and date:	Amended protocol version 6.0 dated January 21, 2019
LINK study ID:	MYR003

Document control

Document Name	Statistical Analysis Plan Amendment 3
Version	1.0
Status	final
Author	Malin Franzon LINK Medical Research Kungsängsvägen 19 SE-753 23 Uppsala, Sweden e-mail: Malin.Franzon@linkmedical.se phone: +46 18 430 31 00 mobile: +46 73 142 11 89

Document history

Version	***Modified by (name and role)***	***Date***	***Description of Changes***
0.1	Malin Franzon, Senior Biostatistician	2020-05-29	Initial version
1.0	Malin Franzon, Senior Biostatistician	2020-06-04	Final version. Updated with comments from sponsor

Table of contents

1 Purpose

The purpose of this amendment (Amendment 3) to the statistical analysis plan (SAP) is to describe changes to the final SAP version 2.0 and the first SAP Amendment dated 2019-05-17 and SAP Amendment 2 dated 2019-08-13.

This SAP Amendment 3 mainly describes tables to be added based on requests during EMA's CHMP assessment of the MAA, which included the report of Interim 1 A-D.

The additional mock tables are included in the updated Data Display Plan (DDP), Final DDP v4.0.

2 Amendment to SAP and prior SAP Amendments (1st SAP Amendment and SAP Amendment 2)

2.1 Presentation of Adverse Events

Adverse Events will be presented as described in the SAP.

However, Overview of Adverse Events, the incidence of Adverse Events and Serious Adverse Events will also be presented by study period (total, during treatment and follow-up) and by subgroups ADA positive/negative.

The following groups of adverse events will be used:

- Adverse events started during the study (both the treatment and FU period)
- Adverse events started during the treatment period
- Adverse events started after the end of treatment period
- Adverse events started during the study (both the treatment and FU period) for the subgroup of ADA positive subjects.
- Adverse events started during the study (both the treatment and FU period) for the subgroup of ADA negative subjects.
- Adverse events started during the treatment period for the subgroup of ADA positive subjects.
- Adverse events started during the treatment period for the subgroup of ADA negative subjects.
- Adverse events started after the end of treatment period for the subgroup of ADA positive subjects.
- Adverse events started after the end of treatment period for the subgroup of ADA negative subjects.

A table with descriptive statistics for time to first injection site reaction in patients with at least one injection site reaction will also be presented by treatment group and Total.

2.2 Other changes and updated DDP

In the amended protocol v 6.0, two interims were planned before the final analysis of all treatment arms.

1) Phase I: When groups A-D have finished, final analysis will be performed for these groups;
2) 24 weeks interim for Phase II (groups E-F);
3) Final analysis: When group E-F (which started after group A-D) have finished, final analyses for all groups (A-F) will be performed.

In the end, the interim 2) with 24 weeks data for E-F was not performed. This is described in an amended protocol v7.0. As the final analysis of groups A-D was based on protocol 6.0, the final analysis for this study will be presented using the endpoints in protocol v6.0.

The DDP has been updated with the changes described in section 2.1 above and the post-hoc analyses described in SAP Amendment 2.

3 Signoff

We have read this SAP Amendment 3 for the MYR 203 study and confirm that, to the best of our knowledge, the statistical analyses to be performed in this study are accurately described.

Hepatera LLC: Yana Deloveri, CEO

SIGNATURE AND DATE

Klaus Junge, External Biostatistician

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LINK Medical Research SAP Author: Malin Franzon, Senior Biostatistician

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17 Signoff

We have reviewed this Data Display Plan (DDP) for the MYR203 study and confirm that, to the best of our knowledge, the statistical analyses to be performed in this study are accurately described.

Hepatera LLC: Yana Deloveri, CEO

SIGNATURE AND DATE

15 · Jun · 2020

Klaus Junge, External Biostatistician

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LINK Medical Research DDP Author: Malin Franzon, Senior Biostatistician

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3 Signoff

We have read this SAP Amendment 3 for the MYR 203 study and confirm that, to the best of our knowledge, the statistical analyses to be performed in this study are accurately described.

Hepatera LLC: Yana Deloveri, CEO

SIGNATURE AND DATE

15 - Jun - 2020

Klaus Junge, External Biostatistician

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LINK Medical Research SAP Author: Malin Franzon, Senior Biostatistician

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