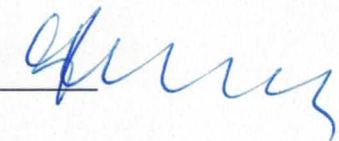# A prospective, randomised, open-label phase IIb clinical trial assessing the effect of pegylated Interferon alfa-2a (Pegasys®) 180 μg once weekly for 48 weeks in addition to an ongoing nucleos(t)ide based treatment on quantitative HBsAg levels in patients with chronic HBeAg-negative hepatitis B – PADD-ON
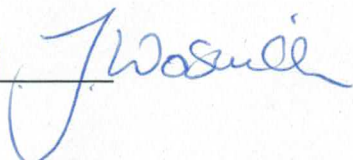
Statistical Analysis Plan

Version 1.0 of Sep 22nd, 2017

Univ.-Prof. Dr. med. P. R. Galle,
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Content

1 Background

1.1 Study Objectives

The primary objective of the trial is to investigate whether the add-on of pegylated interferon alfa-2a to a continued treatment with nucleos(t)ide analogues increases the percentage of patients who have significant decrease (≥ 1 log10) of HBs antigen after 48 weeks.

The secondary objective(s) of the trial are

- To evaluate the safety and tolerability of pegylated interferon alfa-2a when combined with tenofovir, entecavir, lamivudine, adefovir, or a combination of those,
    - Adverse Events (classified into mild/moderate/severe)
    - Vital signs and physical examination
    - Laboratory test abnormalities
    - Laboratory test value changes over time
- To identify biological variables predicting HBs antigen decrease, e.g.:
    - viral genotype
    - time course of HBs antigen level.

Scientific objectives of the trial are

- To determine the effect of pegylated interferon on the frequency and functional properties of HBV-specific cytotoxic and regulatory T-cells in responder and non-responder patients
- To identify potentially predictive biomarkers

1.2 Study Design

The PADD-ON trial is a prospective, randomised, controlled open-label clinical trial with parallel treatment groups. Patients will be randomised (2:1 ratio) either to the treatment group applying weekly interferon injections additionally to basic nucleos(t)ide therapy or to the control group continuing basic nucleos(t)ide therapy without additional trial treatment.

There will be an individual screening period of approximately 4 weeks. After randomisation, the treatment period will take 48 weeks. Follow-up will continue for another 24 weeks.

170 randomized patients are included in the clinical trial, 112 subjects in the treatment group and 58 subjects in the control group.

Flow chart – Treatment group (Pegasys® + nucleos(t)ide)

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15
	Screening	Baseline												EoT	EoFU
	Week -4 to 0	Week 0	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 72
Informed consent	x														
Medical history	x														
Eligibility criteria	x														
12 Lead ECG	x														
Virology	x														
Liver assessment	x														
Drug screening, urinalysis	x														
Pregnancy screening	x				x			x			x			x	
Randomisation		x													
Physical examination[1]	C	T	T	T	T	T	T	T	T	T	T	T	T	C	C
AEs[2], concomitant med.	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Routine laboratory tests[3]	III	I	I	I	II	I	I	II	I	I	I	I	I	II	II
HBV-PCR	x				x			x						x	x
HBs antigen / anti-HBs	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Immunology[4]		x	x	x										x	
Bio-[5] and genetic markers[6]		x[5,6]	x[5]	x[5]	x[5]			x[5]			x[5]			x[5]	x[5]

Flow chart – Control group (nucleos(t)ide only)

	Visit 1	Visit 2			Visit 3			Visit 4			Visit 5			Visit 6	Visit 7
	Screening	Baseline												EoT	EoFU
	Week -4 to 0	Week 0	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 72
Informed consent	x														
Medical history	x														
Eligibility criteria	x														
12 Lead ECG	x														
Virology	x														
Liver assessment	x														
Drug screening, urinalysis	x														
Pregnancy screening	x							x						x	
Randomisation		x													
Physical examination[1]	C	T			T			T			T			C	C
AEs[2], concomitant med.	x	x			x			x			x			x	x
Routine laboratory tests[3]	III	I			II			II			I			II	II
HBV-PCR	x				x			x						x	x
HBs antigen / anti-HBs	x	x			x			x			x			x	x
Immunology[4]		x												x	
Bio-[5] and genetic markers[6]		x[5,6]			x[5]			x[5]			x[5]			x[5]	x[5]

Footnotes:

1. Virology: HCV, HDV, HIV testing; HBe Ag, anti-HBe, anti-HBc

2. Physical examination: "C" is a complete physical examination. "T" is a targeted physical examination including measurements of vital signs, and evaluation of organ systems particularly associated with adverse event(s) symptoms.

3. For patients with early withdrawal from medication, the End of follow-up visit is at 24 weeks after the End of treatment visit.

  I = erythroctes, hemoglobin, hematocrit, platelets, total leukocytes and differential, AST, ALT, total bilirubin, gamma-GT, alkanine phostphatase, total bilirubin (and conjugated bilirubin if total bilirubin is >1.5 x ULN), LDH, sodium, potassium, calcium, creatinine (and calculated clearance), blood urea nitrogen (BUN), uric acid, glucose, PT, INR

  II = erythroctes, hemoglobin, hematocrit, platelets, total leukocytes and differential, AST, ALT, total bilirubin, gamma-GT, alkanine phostphatase, total bilirubin (and conjugated bilirubin if total bilirubin is >1.5 x ULN), LDH, sodium, potassium, calcium, creatinine (and calculated clearance), blood urea nitrogen (BUN), uric acid, glucose, PT, INR, albumin, TSH, fT3, fT4

  III = erythroctes, hemoglobin, hematocrit, platelets, total leukocytes and differential, AST, ALT, total bilirubin, gamma-GT, alkanine phostphatase, total bilirubin (and conjugated bilirubin if total bilirubin is >1.5 x ULN), LDH, sodium, potassium, calcium, creatinine (and calculated clearance), blood urea nitrogen (BUN), uric acid, glucose, PT, INR, albumin, TSH, fT3, fT4, AFP, IgG, ANA, SMA, SLA, LKM, AMA, ANCA, ferritin, lipid profile (triglycerides, total cholesterol, HDL, LDL), HLA typing, urinalysis

4. Immunology/Immune monitoring: Blood samples (50 mL each) for PBMC purification and immune monitoring

5. Biomarkers: blood samples of 15-20 mL each, serum samples to be stored at -80 °C

6. Genetic Markers: 2 vials of 2 mL EDTA blood to be frozen in liquid nitrogen and stored at -80°C.

2 Analysis Populations

2.1 Definitions

All subjects who signed informed consent / were assigned a randomisation number are considered as enrolled/randomised subjects, even if there are no assessments of the analysis variables.

All randomised subjects with at least one available post-baseline assessment of the primary analysis variable will be included in the modified Intention-to-treat (mITT) population. Within mITT population analyses subjects will be assigned to the treatment to which they were randomised. The mITT definition from the study protocol was modified as the wording "all subjects who received at least one dose of trial treatment" would include only patients from the interferon group into the mITT population.

All subjects of the mITT population without major protocol violations will be included in the Per Protocol (PP) population. Major protocol violations are described in section 2.3.

The safety population comprises all randomised subjects who received at least one dose of nucleos(t)ide based treatment. In analyses of the safety population subjects will be assigned to the treatment which they actually received.

Patient 09/004 will be excluded from the analyses in the mITT and the PP population as important inclusion criteria were violated (patient is HBeAg positive).

2.2 Scope

The analyses of efficacy will be based primarily on the mITT population.

The primary analysis population for the secondary endpoints except for safety data is the mITT population.

All summaries and tables of safety data will be performed for the safety population.

Supportive analyses for primary and secondary endpoints will be performed in the PP population.

All data of the enrolled population will be listed.

2.3 Major Protocol Violations

The following criteria will be regarded as major protocol violations. The subjects showing at least one of these major protocol violations will be excluded from the PP Population:

- Violation of inclusion criteria

- Meeting any exclusion criteria

- Concomitant treatment with not permitted medication.
  The following concomitant treatments are not permitted during the trial (according to the protocol):

  - Telbivudine

  - Systemic corticosteroids, if used for longer than 14 days, or other immunsuppressive medications (e.g. cyclosporines, tacrolimus, methotrexate etc.)

  - Systemic cytostatic chemotherapy

  - Immune-modulating agents such as IL-2, anti-TNF-antibodies or rituximab

  - Nephrotoxic agents such as aminoglycoside antibiotics, amphotericin B, foscarnet, ganciclovir, NSAID, or other agents with significant nephrotoxic potential

  - Hepatotoxic agents such as anabolic steroids, isoniacid, itraconazole, ketoconazole, rifabutin, rifampin, or other agents with significant hepatotoxic potential

- Compliance less than 90%

- Trial treatment not as randomised

3 Study Centres

Recruitment and treatment of subjects is performed in 24 trial centres in Germany.

4 Analysis Variables

4.1 Demographics

The following demographic data will be documented:
- Age and date of birth,
- Gender (female/male),
- ethnic origin/nationality (European/Asian/African/Other),

4.2 Baseline characteristics

- Virology before screening (HBV DNS (IU/mL), HBV DNS negative (Y/N), HBsAg (IU/mL)
- Virology (screening): HBV DNS (IU/mL), HBV DNS negative (Y/N), HBsAg (IU/mL); anti-HBs, HBeAg, Anti-HBe, Anti-HBc, HCV, HDV, HIV (positive/negative)
- HBV disease characteristics: HBV genotype (A-H/ wildtype; if available), samples for serological assessment of HBV genotype (Y/N; if not available)

- Urine drug screening (positive/ negative; if available) and urinalysis (normal/abnormal, clinically not relevant/abnormal, clinically relevant; if available)
- Urine pregnancy test for women of childbearing potential (negative/ positive/ sterile or postmenopausal)
- Medical History: Relevant previous illnesses (Y/N), possible source and assumed year of infection (perinatal, injection drug use, sexual, occupational, transfusion, unknown, other), year of first diagnosis
- Imaging of the liver (if available): method (ultrasound/ CT scan/MRI),, presence of hepatocellular carcinoma (Y/N), extent of fibrosis (0-6/ unknown), liver elastography (kPa)
- Liver assessment (if available): Results from liver biopsy, extent of fibrosis (0-6/ unknown)
- Alcohol consumption > 20g/d (women)/ >30g/d (men) (Y/N)
- 12-lead resting-ECG measurement (normal/abnormal, clinically not relevant/ abnormal, clinically relevant/ not done)
- Fundoscopy (normal/ abnormal, clinically not relevant/ abnormal, clinically relevant/ not done)
- General physical examination (screening): Different organ systems (normal/ abnormal, clinically not relevant/ abnormal, clinically relevant/ not done)
- Routine laboratory test (screening): hematology and clinical chemistry III)
- Vital signs (baseline): blood pressure, pulse, temperature, height (cm, only at screening), body weight (kg), BMI (kg/m²)
- Samples for immunology (baseline): biomarker (Y/N), genetic marker (Y/N), immunology (Y/N)
- Targeted physical examination (baseline):Neurologic symptoms (Y/N), neuropathy (Y/N), proofed by neurologist (Y/N))

Additionally, it is documented whether a re-screening was done. If yes, screening values will be replaced by re-screening values.

4.3 Primary variable

The primary endpoint is the objective response after 48 weeks of combination therapy. The response is defined as a confirmed reduction of ≥1log10 in HBs antigen compared to baseline.

4.4 Secondary variables

4.4.1 Efficacy

Efficacy analyses are based on the measurements of HBs antigen and anti HBs concentration which will be done at screening, at baseline and on a regular basis during the 48 week treatment phase (every four weeks in the interferon arm and every twelve weeks in the control arm) as well as at end of follow-up (week 72).
Secondary efficacy endpoints are:
- Decline of quantitative HBs antigen at week 12 and 24
- Rate of patients with at least 10% HBs antigen loss at week 24 compared to baseline
- HBsAg seroconversion defined as percentage of subjects who become HBsAg negative and anti-HBs positive during the observation period
- HBs antigen levels at all measurement times

4.4.2 Safety / Tolerability

Adverse events and concomitant medication will be documented continuously during the study.

Laboratory data will be evaluated at every study visit; the following parameters will be assessed:

Screening (panel III):

erythroctes, hemoglobin, hematocrit, platelets, total leukocytes and differential, AST, ALT, total bilirubin (and conjugated bilirubin if total bilirubin is >1.5 x ULN), bilirubin ratio (direct/ indirect), gamma-GT, alkanine phosphatase, LDH, sodium, potassium, calcium, creatinine (and calculated clearance), blood urea nitrogen (BUN), uric acid, glucose, PT, INR, albumin, TSH, fT3, fT4, AFP, IgG, ANA, SMA, SLA, LKM, AMA, ANCA, ferritin, lipid profile (triglycerides, total cholesterol, HDL, LDL), HLA typing, urinalysis

Week 12, 24, 48 and 72 (panel II):

erythroctes, hemoglobin, hematocrit, platelets, total leukocytes and differential, AST, ALT, total bilirubin (and conjugated bilirubin if total bilirubin is >1.5 x ULN), bilirubin ratio (direct/ indirect), gamma-GT, alkanine phosphatase, total bilirubin (and conjugated bilirubin if total bilirubin is >1.5 x ULN), LDH, sodium, potassium, calcium, creatinine (and calculated clearance), blood urea nitrogen (BUN), uric acid, glucose, PT, INR, albumin, TSH, fT3, fT4

Week 0, 4, 8, 16, 20, 28, 32, 36, 40, 44 for IFN patients and Week 0 and 36 for control patients (panel I):

erythroctes, hemoglobin, hematocrit, platelets, total leukocytes and differential, AST, ALT, total bilirubin (and conjugated bilirubin if total bilirubin is >1.5 x ULN), bilirubin ratio (direct/ indirect), gamma-GT, alkanine phosphatase, LDH, sodium, potassium, calcium, creatinine (and calculated clearance), blood urea nitrogen (BUN), uric acid, glucose, PT, INR

The following vital signs will be evaluated at every study visit:

Body temperature, heart rate, blood pressure, weight and BMI (height only at screening)

Urine pregnancy tests will be performed for women with childbearing potential at screening and EoT for both groups, at week 12, 24, 36 and 48 in the treatment group and week 48 in the control group.

Cardiologic evaluation by 12-lead ECG will be done at screening.

A complete physical examination including vital signs will be done at screening, end of treatment (EoT) and end of follow-up (EoFU). A targeted physical examination will be done at baseline, and every four or twelve weeks in the interferon or control arm, respectively.

HBV-PCR will be performed at week 0, 12, 24, 48 and 72.

5 Treatment of Missing Values and Outliers

5.1 Missing values

The last observation carried forward method (LOCF) will be used for the handling of missing data due to drop-out when analysing the primary endpoint.

LOCF for primary analysis: In order to avoid bias and ensure the comparability of the two treatment groups, only data from visits which took place after similar time intervals in the two groups will be included in the primary analysis (visits in week 12, 24, 36 and 48), meaning that only HBsAg values potentially obtained at week 12, 24 or 36 will be carried forward in case of missing values at week 48. There will be no baseline values carried forward.

Modified LOCF for sensitivity analysis: All LOCF analyses will be repeated with the LOCF method applied to the last visit available meaning that in the interferon group every last visit (except the baseline visit) can be carried forward, not only the ones in week 12, 24 or 36.

5.2 Outlier

There will be no methods employed for detecting outliers.

6 Statistical Analyses

The default summary statistics for quantitative variables will be the number of observations (n), mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), minimum and maximum for those patients with data available.

For qualitative variables, the number (n) and percentage (%) of patients with non-missing data per category will be the default summary presentation. If appropriate, the number of missing values will be displayed as a "Missing" category.

All variables will be displayed by treatment group and with a total column.

Listings of all data available will be provided.

6.1 Disposition of Patients

The following patient disposition variables will be presented by numbers and percentages:

- Informed consent given to study participation / study treatment
- Informed consent given to biomarker analysis
- Informed consent given to genotypic analysis
- Informed consent given to transfer of anonymised biomaterial
- Inclusion and exclusion criteria
- Size of analysis populations (Safety, mITT, PP)
- Study completion according to protocol
- Main reason for premature discontinuation of study treatment
- Follow-up visit according to protocol (interferon group)
- Main Reason for follow-up visit not according to protocol (interferon group)
- Participation at every study visit (if the date is available, participation at the visit is assumed)
- Participation at every main study visit (screening, week 0, 12, 24, 36, 48 and 72)
- Type of protocol violation

6.2 Demographics and Baseline characteristics

All parameters (except date of birth, virology before screening, HBV-DNA [IU/mL] at screening, assumed year of infection and year of first diagnosis) mentioned in chapter 4.1 and 4.2 will be summarised descriptively. Appropriate exploratory p-values of t-test (unequal variances) or chi-square test to test on differences between treatment groups will be shown.

Additionally the time since infection will be calculated by:

(year of screening – year of infection) + 1.

If date of infection differs from date of first diagnosis, the time since first diagnosis will be calculated as well:

(year of screening – year of first diagnosis) + 1.

Exploratory p-values of t-test (unequal variances) to test on differences between treatment groups will be shown.

6.3 Prior and Concomitant Diseases

Concomitant diseases will be coded by MedDRA (Medical Dictionary for Regulatory Activities) terminology and presented by number and percentages within preferred term and system organ class.

The number of patients with at least one concomitant disease will be displayed by number and percentages.

6.4 Prior and Concomitant Medication

Concomitant medication will be coded using the current WHO drug dictionary version and will be presented within ATC-2 and ATC-4 level.

Concomitant medication for HBV (basic nucleos(t)ide treatment) and concomitant medication not for HBV will be documented and tabulated separately.

Patients with at least one concomitant medication will be displayed by number and percentages.

6.5 Extent of Exposure to Study Treatment / Compliance

Extent of exposure: The dose of injection is documented for the interferon treatment arm on a weekly basis. Descriptive statistics will be provided for the overall cumulative dose.

Compliance will be calculated by dividing the number of used interferon injections by the planned number of injections. This number is set to 47 (most patients did not receive another injection in week 48 where the EoT visit took place). Still a higher number than 47 injections in total is possible as in certain cases the EoT visit took place after more than 48 weeks. (. This parameter will be used as compliance parameter for definition of major protocol violation.

Additionally, the number of visits without re-screening and follow-up visits will be calculated per patient and treatment group. Descriptive statistics and exploratory p-value (t-test with unequal variances) will be provided for the number of visits per patient given as percentage based on all possible visits per treatment group until EoT (interferon group: 14 visits, control group: 6 visits).

6.6 Primary Analysis

Null hypothesis: $HBsAgRR_{Interferon} = HBsAgRR_{Control}$

Alternative hypothesis: $HBsAgRR_{Interferon} \neq HBsAgRR_{Control}$

HBsAgRR denotes HBs antigen response rates. The subscripts show the respective treatment group.

Response is defined as significant decrease (≥ 1 log10) of HBs antigen after 48 weeks compared to baseline. The response rates will be compared between the treatment groups by

Fisher's exact test (two-sided, level of significance α=0.05). Additionally a Cochran-Mantel-Haenszel test stratifying for screening HBsAg levels will be performed, if the number of patients in the respective strata is sufficient. The primary analysis population is the modified Intention to treat population.

Subjects with missing HBsAg measurements at week 48 (EoT) will be analysed according to the LOCF principle in the primary analysis as specified in section 5.1 ("LOCF for primary analysis). This approach is considered slightly conservative but allows including all patients with at least one valid HBsAg measurement in week 12, 24, 36 or 48 to be included into the confirmatory modified Intention to treat analysis. The analysis will be repeated with the modified LOCF approach specified in section 5.1 ("LOCF for sensitivity analysis").

Further supportive analyses are planned:

The primary analysis will be repeated using all available data as observed (no LOCF will be applied). Drop-outs before week 48 will be considered as non-responders.

Also the primary analysis (Fisher's exact test, Cochran-Mantel-Haenszel test) will be repeated for the PP population with and without application of the LOCF method (both LOCF definitions).

As sensitivity analysis a logistic regression model including the factor treatment and the covariate HBsAgScreen (HBsAg level at screening < 20.000IU/ mL vs. ≥ 20.000 IU/mL) will be applied on each analysis population.

Furthermore, a logistic regression model including covariates assumed to predict treatment response (age, sex, duration of antiviral therapy before the study) will be applied.

6.7 Secondary Analyses

6.7.1 Efficacy

The primary population for the analyses of efficacy is the mITT Population. If there is a difference of at least 5% between PP population and mITT population regarding the number of patients, all secondary efficacy analyses will be repeated for the PP population.

All hypotheses will be tested on a two-sided level of significance α=0.05 and results will be interpreted in an exploratory manner.

Missing values will not be replaced.

6.7.1.1 HBs antigen at week 12 and 24

The decline of quantitative HBs antigen at week 12 and 24 will be analysed using an ANCOVA model, including treatment and baseline HBs antigen as parameters in the model.

6.7.1.2 HBs antigen rate at week 24

The rate of patients with at least 10% HBs antigen loss at week 24 compared to baseline will be analysed by Fisher's exact test (results of interim analysis). Drop-outs before week 24 will be considered as non-responders.

6.7.1.3 HBs antigen seroconversion

HBs antigen seroconversion is defined as percentage of subjects who become HBs antigen negative (< 10 IU/ml) and anti-HBs positive (≥10 IU/l) at least once during the observation period (baseline - EoFU). In order to compare the two treatment groups a Cochran-Mantel-

Haenszel test or Fisher's exact test will be performed (depending on the number of patients in the respective strata).

Additionally, patients with HBs antigen seroconversion will be displayed by group and visit. This will be repeated for all patients who become HBs antigen negative.

6.7.1.4   HBs antigen over time

The HBs antigen concentration and changes to baseline will be analysed descriptively by visit. Whenever applicable, exploratory p-values (t-test) for the comparison between treatment groups will be provided. Mean antigen concentrations per time will also be displayed graphically. Additionally, a spaghetti plot will be produced that depicts the HBs antigen concentration over time for each individual.

6.7.2   Safety / Tolerability

6.7.2.1   Adverse Events

Frequencies of subjects experiencing at least one adverse event (AE) will be displayed by body system and preferred term according to MedDRA terminology. Detailed information collected for each AE will include: A description of the event, duration, whether the AE was serious, intensity, relationship to trial drug, action taken, clinical outcome.

Frequencies of patients experiencing at least one serious adverse event (SAE) will be displayed by body system and preferred term according to MedDRA terminology.

Further tables will present the number of subjects observed with AEs specified by event intensity and relationship to trial drug.

A summary table will be produced showing the number of patients with
- any AEs
- any SAEs
- any fatal AEs

- any severe AEs
- any related AEs
- any related severe AEs
- any related serious AEs
- any fatal related AEs
- any AEs leading to premature study discontinuation
- any AEs leading to actions regarding the study medication

6.7.2.2   Laboratory Parameters

Listings will be prepared for each laboratory parameter and will be structured to permit review of the data per subject as they progress on treatment.

Summary tables will be prepared to examine the changes of laboratory parameters over time. Laboratory measurements and the changes to baseline will be analysed descriptively by visit. Exploratory p-values (t-test or chi-square test) will be shown whenever applicable.

Additionally, shift tables will be provided to examine the changes of laboratory data (clinically relevant Y/N) from baseline to EoT and from baseline to EoFU.

6.7.2.3   Vital Signs

Vital signs (blood pressure, heart rate, weight, BMI and temperature) and corresponding changes to baseline in vital signs will be analysed descriptively by distributional parameters (such as mean and standard deviation).

Exploratory p-values for the comparison of treatment groups will be provided, whenever applicable.

6.7.2.4 Physical examination

Results of the complete physical examination and the targeted examination will be tabulated by visit, respectively. Exploratory p-values (chi-square test) for the comparison of treatment groups will be shown.

6.7.3 Other analyses

Blood samples for immune monitoring / immunology, for bioinformatics analysis of genetic markers will be obtained at the baseline visit. Blood samples for identification of biomarkers will be obtained every four or twelve weeks respectively in the interferon or control arm, respectively. The corresponding analyses, for example the identification of potentially predictive biomarkers will not be carried out by the IZKS.

6.8 Subgroup analyses

Age, sex, level of quantitative HBsAg at baseline, nucleos(t)ide regimen (substances at baseline, combination, duration) will be subject to subgroup analyses for the primary endpoint.

If appropriate, logistic regressions will be applied, including treatment, subgroup parameter and interaction between treatment and subgroup parameter in the model.

6.9 Interim Analyses

There will be no interim analysis in the sense that the primary endpoint is analysed prematurely and a decision about the continuation of the study is derived.

However, it is planned to compare the rates of patients with at least 10% HBsAg loss 24 weeks after the start of study treatment compared to baseline between the treatment groups as soon as these data are available. The analysis will be interpreted in an explorative manner. Therefore no adjustment of the significance level is required.

The influence of this premature analysis on the primary analysis and the predictability of the results of the primary analysis based on the results of the premature analysis are expected to be limited for the following reasons:

- The recruitment phase will be terminated at the time point of the premature analysis.

- According to the expected accrual time, the analysis will be performed only around 16weeks before the end of treatment of the last patient.

- The loss rates in the early response analysis (at least 10% HBsAg loss) and the primary analysis (reduction of at least 1log10 HBsAg) are defined differently.

Details of the interim analysis are documented in an additional SAP.

7 Software

All analyses will be performed using the Statistical Analysis Software (SAS), Version 9.4.

8 Appendix

8.1 Planned Tables

No	Title	Population
	Patient Disposition (including In- and Exclusion Criteria)	Enrolled
	Patient Discontinuation	Randomised
	Important Protocol Violations	Randomised
	Demographics and Baseline Characteristics	mITT/ PP
	Concomitant Diseases	mITT
	Concomitant Medication	mITT
	Concomitant Medication for HBV (Basic Nucleos(t)ide Treatment)	mITT
	Exposure to Study Medication	mITT
	Compliance (Based on Used Medication)	mITT
	Compliance (Based on Visits)	mITT
	Primary Analysis: Comparison of Responder Rates after 48 Weeks (LOCF)	mITT/ PP
	Sensitivity Analysis: Comparison of Responder Rates after 48 Weeks (modified LOCF)	mITT/ PP
	Sensitivity Analysis: Comparison of Responder Rates after 48 Weeks (no LOCF)	mITT/ PP
	Sensitivity Analysis: Logistic Regression of Responder Rates after 48 Weeks	mITT/ PP
	Secondary Analysis: Decline of HBsAg Concentration at Week 12 and Week 24	mITT/ (PP)*
	Secondary Analysis: Rate of Patients with at least 10% HBsAg Loss after 24 Weeks	mITT/ (PP)*
	Secondary Analysis: Subjects with HBsAG seroconversion (overall)	mITT
	Secondary Analysis: Subjects with HBsAG seroconversion (over time)	mITT
	Secondary Analysis: Subjects becoming HBsAG negative (overall)	mITT
	Secondary Analysis: Subjects becoming HBsAG negative (over time)	mITT
	Secondary Analysis: HBsAG Concentration and Changes to Baseline by Visit	mITT/ (PP)*

	Adverse Events (Summary Table)	Safety
	Adverse Events	Safety
	Serious Adverse Events	Safety
	Adverse Events by Severity (Group A)	Safety
	Adverse Events by Severity (Group B)	Safety
	Adverse Events by Relationship to Trial Medication (Group A)	Safety
	Adverse Events by Relationship to Trial Medication (Group B)	Safety
	Laboratory Parameters over Time (Summary Table)	Safety
	Laboratory Parameters– Changes to Baseline	Safety
	Shift Tables: Changes of Laboratory Data (Clinical Relevant Y/N) from Baseline to EoT and EoFU	Safety
	Vital Signs over Time (Summary Table)	Safety
	Complete physical Examination (Summary Table)	Safety
	Targeted Physical Examination (Summary Table)	Safety
	Blood Samples for Immunology/ Markers	Safety
	Subgroup Analyses: Logistic Regression of Responder Rates after 48 Weeks	Safety

*Analyses in the PP population will only be carried out if the number of patients differs > 5% between mITT and PP population.