Official Title: A Phase II Comparative, Open Label, Randomized, Multicenter, China-Only Study to Investigate the Pharmacokinetics, Efficacy and Safety of Subcutaneous Rituximab Versus Intravenous Rituximab, Both in Combination With CHOP in Previously Untreated Patients With CD20 Positive Diffuse Large B Cell Lymphoma

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STATISTICAL ANALYSIS PLAN

TITLE: **A PHASE II COMPARATIVE, OPEN LABEL, RANDOMIZED, MULTICENTER, CHINA-ONLY STUDY TO INVESTIGATE THE PHARMACOKINETICS, EFFICACY AND SAFETY OF SUBCUTANEOUS RITUXIMAB VERSUS INTRAVENOUS RITUXIMAB, BOTH IN COMBINATION WITH CHOP IN PREVIOUSLY UNTREATED PATIENTS WITH CD20 POSITIVE DIFFUSE LARGE B CELL LYMPHOMA**

PROTOCOL NUMBER: YO42207

STUDY DRUG: Rituximab (RO0452294) (MabThera®)

VERSION NUMBER: 1.0

IND NUMBER: Not applicable

EUDRACT NUMBER: Not applicable

SPONSOR: F. Hoffmann-La Roche Ltd

PLAN PREPARED BY: [redacted]

DATE FINAL: See electronic date stamp on the last page of this document

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1. BACKGROUND

This Statistical Analysis Plan (SAP) provides details of the planned analyses and statistical methods for Study YO42207 “a Phase II comparative, open label, randomized, multicenter, China-only study to investigate the pharmacokinetics, efficacy and safety of subcutaneous rituximab versus intravenous rituximab, both in combination with CHOP in previously untreated patients with CD20 positive diffuse large B cell lymphoma”.

Study BO22334, a global two-stage Phase III trial, has demonstrated non−inferiority of trough serum concentrations [C_{trough}] at Cycle 7 (Stage 1 primary endpoint). Non-inferior C_{trough} with the fixed rituximab SC dose of 1400 mg was demonstrated compared with rituximab IV 375 mg/m^2 given every 3 weeks. The ratio $C_{trough,SC}/C_{trough,IV}$ at Cycle 7 was 1.62 (90% CI: 1.36,1.94)) with comparable variability (coefficient of variation [CV] 43.2% in the rituximab SC arm and CV 36.7% in the rituximab IV arm). The geometric mean AUC was also higher in the rituximab SC arm, with observed rituximab serum $AUC_{(SC)}/AUC_{(IV)}$ ratio during Cycle 7 of 1.38 (90% CI: 1.24,1.53) and comparable variability between the two arms (coefficient of variation [CV] 33.7% in the rituximab SC arm and CV 28.0% in the rituximab IV arm). Study BO22334 has also shows comparable Objective response rate (ORR) based on the investigator assessments (84.9% (95% CI: 79.2%, 89.5%) in the rituximab IV arm versus 84.4% (95% CI: (78.7%, 89.1%) in the rituximab SC arm.

Rituximab IV and SC have a well-established benefit-risk profile and are approved in more than 90 countries or regions. The SC formulation is expected to bring significant and clinically meaningful benefits to Chinese patients in terms of improved tolerability with potentially fewer and less severe administration-related reactions (ARRs).

The purpose of Study YO42207 is to evaluate pharmacokinetics, efficacy and safety of subcutaneous rituximab in a randomized, controlled, and comparative setting for Chinese patients with CD20 positive diffuse large B cell lymphoma. This study will explore the efficacy of rituximab SC and rituximab IV, respectively, in previously untreated DLBCL patients, based on the complete response rate (CRR) observed with each formulation.

2. STUDY DESIGN

This is a Phase II, multicenter, randomized, controlled, open-label, China-only study to investigate the PK, efficacy, and safety of rituximab SC in combination with CHOP versus rituximab IV in combination with CHOP in previously untreated patients with CD20 positive DLBCL.

This study will be conducted at approximately 8 sites in China and will approximately enroll 50 patients. Eligible patients will be stratified according to IPI scores (IPI 0-2 versus IPI 3-5) and randomized at a 1:1 ratio into the following two treatment groups (crossover to the experimental arm is not permitted):

- R^{SC}-CHOP: Cycle 1 rituximab IV plus seven cycles of rituximab SC in combination with six or eight cycles of CHOP chemotherapy administered every 3 weeks; rituximab IV will be used at the standard dose of 375 mg/m^2 and rituximab SC will be given at a dose of 1400 mg as confirmed in the Phase III Study BO22334.

- R^{IV}-CHOP: Eight cycles of rituximab IV in combination with six or eight cycles of CHOP chemotherapy administered every 3 weeks; rituximab IV will be used at the standard dose of 375 mg/m^2.

Figure 1 Dose schema

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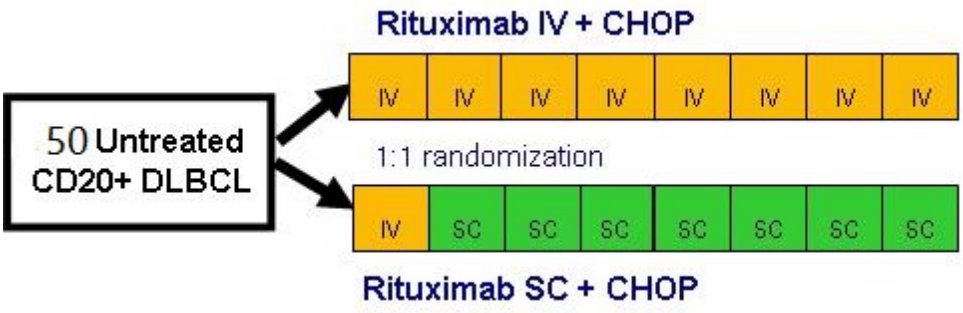

After the end of study treatment, patients will be followed-up every 3 months for 6 months (i.e., 12 and 24 weeks after the last dose of study treatment).

Patients will be assessed for disease response by the investigator and IRC according to the Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014). PET-CT and dedicated CT scans will be obtained at screening and 6-8 weeks after completion of study treatment, or sooner in the event that a patient discontinues early. An interim assessment will be obtained after Cycle 4 and should include PET-CT and dedicated CT. If local practice prohibits obtaining both assessments after Cycle 4, PET-CT alone (preferred) or CT alone may be obtained at this time point. During the follow-up period, imaging (may be CT only) will be performed every 3 months, i.e., Week 12 and 24 after last treatment, in accordance with study visits and will include the neck (if involved at baseline), chest, abdomen, and pelvis.

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix 1. For additional details, see the Schedule of Assessments in Appendix 2.

2.2 ENDPOINTS

2.2.1 Primary Pharmacokinetic Endpoints

The primary objective of this study is to demonstrate the non-inferiority of rituximab serum C_{trough} obtained at Cycle 7, 21 days after SC administration, with that obtained at Cycle 7, 21 days after IV administration on the basis of the following endpoint:

- Ratio of $C_{trough,SC}/C_{trough,IV}$ during Cycle 7

2.2.2 Secondary Pharmacokinetic Endpoints

- Ratio of AUC_{SC}/AUC_{IV} during Cycle 7
- Other PK parameters, such as AUC and C_{trough} at other treatment cycles, maximum serum concentration (C_{max}), total clearance, volume of distribution at steady state, and terminal half-life ($t_{1/2}$) (if feasible or appropriate) as appropriate

2.2.3 Key Efficacy Endpoints

- Complete response rate (CRR) at the end of the study treatment, as determined by the Independent Review Committee (IRC) using Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014)

2.2.4 Secondary Efficacy Endpoints

- Objective response rate (ORR), defined as CR or partial response (PR) at the end of the study treatment, as determined by investigator and IRC using Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014)
- CRR (CR, CRu) at the end of study treatment, as determined by IRC using International Working Group (IWG) Response Criteria for NHL 1999 Guidelines
- CRR at the end of the study treatment, as determined by the investigator using Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014)

2.2.5 Safety Endpoints

- Safety outcomes as assessed by adverse events, including rituximab administration-related reactions (ARRs), laboratory assessments, and vital signs; and immunogenicity as assessed by anti-rituximab antibodies and anti-rHuPH20 antibodies

2.3 DETERMINATION OF SAMPLE SIZE

Under the assumption of a coefficient of variation equal to 0.5 and assuming that the true C_{trough} of rituximab SC formulation is 20% above the rituximab IV formulation (i.e., mean $C_{trough,SC}$ to be 20% above $C_{trough,IV}$), 20 patients in each treatment arm are needed in order to achieve 80% power with one-sided alpha of 0.05 (i.e., 2-sided 90% CI). Assuming that 20% of patients would not have valid PK data at Cycle 8 pre-dose, a total of approximately 50 patients will be enrolled into the study (see Table 1).

Table 1 Sample Size for Primary Endpoint (i.e., Non-inferiority in C_{trough})

Parameter	Value
Test significance levels, α (one-sided)	0.050
Lower equivalence limit for μ_T/μ_S, Δ_L	0.800
Expected ratio, μ_T/μ_S	1.200
Coefficient of variation, σ_S/μ_S	0.500
Power (%)	80
Number of patients per group	18 (rounded to 20)
Number of patients (total)	36 (rounded to 40)

2.4 ANALYSIS TIMING

Primary analysis will be conducted when all the patients have been evaluated for the tumor response at the end of treatment visit. The final analysis will be performed at the end of study.

3. STUDY CONDUCT

3.1 RANDOMIZATION

Patients who are eligible for study entry are randomly assigned (1:1) to either R^{SC}-CHOP arm or R^{IV}-CHOP arm via the interactive voice or Web-based response system (IxRS) through use of a permuted block randomization scheme.

Randomization procedures use one stratification factor:

- IPI Scores (IPI 0-2 versus IPI 3-5)

3.2 INDEPENDENT REVIEW FACILITY

An IRC composed of certified radiologists and a hematologist or oncologist with experience in malignant lymphoma will assess all patients for response according to Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014) (see protocol Appendix 3) and IWG Response Criteria for NHL 1999 Guidelines, respectively, on the basis of imaging results and biopsy results that are performed related to efficacy evaluation. Decisions will be guided by a Charter specific to the independent review.

4. STATISTICAL METHODS

4.1 ANALYSIS POPULATIONS

4.1.1 Intent-to-Treat Population

The intent-to-treat (ITT) population consists of all randomized patients. Patients are assigned to the treatment group to which they were randomized. The ITT population will be used for the efficacy analyses.

4.1.2 Pharmacokinetic-Evaluable Population

PK analyses will be based on all patients with at least one PK assessment. PK analyses will be analyzed as treated. Patients will be excluded from the PK analysis population if they significantly violate the inclusion or exclusion criteria, deviate significantly from the protocol, or if data are unavailable or incomplete, where the PK analysis might be influenced. Excluded cases will be documented, including the reason for exclusion. All decisions on exclusions from the analysis will be made prior to database closure.

4.1.3 Per Protocol PK Population

The Per Protocol PK (PPP) analysis population will include all patients enrolled who adhered to the protocol. Patients will be assigned to treatment groups as treated.

Exclusions from the Per Protocol PK analysis populations will be made for the following reasons:

- Patients are missing the C_{trough} during Cycle 7 (pre-dose Cycle 8 PK) sample,
- Patients with a Cycle 7 C_{trough} sample collected with more than 3 days deviation from the planned date on Day 22 (i.e., before Day 19 or after Day 25),
- Patients given a dose amount that deviates from the planned dose by >20% within 3 cycles (from Cycle 5),
- Patients with a Cycle 7 dose delay of more than 7 days,

- Assay error impacting Cycle 7 C_{trough} (pre-dose Cycle 8) measurement.

Patients will be excluded from the PK endpoint analyses according to the exclusions defined above. Excluded cases will be documented, including the reason for exclusion. All decisions on exclusions from the analysis will be made prior to database closure.

The Per Protocol PK (PPP) analysis population will be used for the primary endpoint of ratio of $C_{trough,SC}/C_{trough,IV}$ during Cycle 7 and the secondary PK endpoint of ratio of observed rituximab area under the serum concentration curve of Cycle 7 (AUC_{SC}/AUC_{IV}).

4.1.4 Safety Population

The safety analysis population consists of all randomized patients who received at least one dose of study drug, with patients grouped according to treatment received.

4.1.5 Immunogenicity Population

The immunogenicity analysis population will consist of all patients with at least one anti-drug antibody (ADA) assessment. The ADAs include anti-rituximab antibodies and anti-rHuPH20 antibodies. Patients will be grouped according to treatment received or, if no treatment is received prior to study discontinuation, according to treatment assigned.

4.2 ANALYSIS OF STUDY CONDUCT

The number of patients who randomize, receive treatment, complete study treatment, discontinue from study will be summarized by treatment group. Reasons for premature study treatment discontinuation will be listed and summarized by treatment group. Reasons for study discontinuation will be listed and summarized by treatment group. Enrollment and major protocol deviations will be listed and summarized by treatment group.

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics (such as age, sex, race, weight, height, BSA) will be summarized by treatment arm for the ITT population.

Baseline disease characteristics (such as ECOG Performance Status, IPI Score, time since initial DLBCL, Ann Arbor Stage at diagnosis, Ann Arbor Stage at study entry) will also be summarized by treatment arm for the ITT population.

Baseline measurements are the last available data obtained prior to patients receiving the first dose of study drug, unless otherwise noted.

Continuous variables will be summarized using number of patients, means, standard deviations, medians and range, and categorical variables will be summarized using counts and proportions, as appropriate. Summaries will be presented overall and by treatment arm for the ITT population.

4.4 PHARMACOKINETIC ANALYSES

For all patients, C_{trough} will be measured at Cycle 7 (i.e. pre-dose Cycle 8) and will be the basis of the primary analysis. PK parameters of rituximab will be estimated using standard non-compartmental analysis and reported in the CSR.

4.4.1 Pharmacokinetic Primary Endpoint

The primary PK endpoint is the ratio of observed $C_{trough,SC}/C_{trough,IV}$ during Cycle 7. The serum rituximab C_{trough} at Cycle 7 will be measured at pre-dose of Cycle 8. The lower limit of the two-sided 90% CI should be above 0.80 in order to show non-inferiority of $C_{trough,SC}$ versus $C_{trough,IV}$. The primary analysis of C_{trough} will be based on logarithmic values to compensate for the skewness of the distribution. According to Berinstein et al., a strong dependence of C_{trough} levels from baseline tumor load has been noted and therefore, an analysis of covariance model will be used to adjust for tumor load at baseline and the tumor load was defined as SPD of all entered indicator lesions at baseline:

$$ln\left(C_{trough}\right) = \mu + \tau + BTL + \varepsilon$$

Where:

$ln\left(C_{trough}\right)$, the log-transformed C_{trough} value

μ, the overall mean effect

τ, the treatment effects

BTL, the tumor load at baseline

ε, a random error with normal distribution N(0,1)

The above model will be performed using SAS procedure MIXED:

```
ods output LSMeans=lsmeans Diffs=diffs;
 proc mixed data=<data> alpha=0.1;
 class <treatment code>;
 model <logarithmic estimated Ctrough>=<treatment code> <tumor load at baseline>;
 lsmeans <treatment code>/alpha=0.1 cl diff pdiff;
 run;
 quit;
 ods output close;
```

Both the LSmean of logarithmic C_{trough} with its 90% CI and the treatment difference of LSmean with its 90% CI will be estimated. Then Geometric mean (90% CI) of C_{trough} for each treatment and Geometric mean ratio (90% CI) of $C_{trough,SC}/C_{trough,IV}$ can be calculated by back-transformed using the exponential function.

For no adjusted ratio on tumor load, the two one-sided tests (TOST) equivalence test of Schuirmann will be used for C_{trough} value on original scale with lognormal distributional assumption. The equivalence bounds of geometric mean C_{trough} ratio is set to between 0.8 and 1.25. Geometric mean ratio (90% CI) of $C_{trough,SC}/C_{trough,IV}$ and the coefficient of variation will be estimated using SAS Procedure TTEST:

```
ods output EquivLimits=equivlimits EqulvaTests=equlvtests;
proc ttest data=<data> alpha=0.05 test=ratio dist=lognormal tost(0.8, 1.25);
  class <treatment code>;
  var <estimated Ctrough>
```

run;

The following supplemental analysis will be added to support primary analysis and will be analyzed on Pharmacokinetic-Evaluable Population:

1) Include all patients who have received at least 4 cycles of Rituximab IV/SC with at least one observed C_{trough} from Cycle 4 to Cycle 7. The serum rituximab C_{trough} during each cycle will be measured at pre-dose of the next cycle. The ratio of observed $C_{trough,SC}/C_{trough,IV}$ during Cycle 7 will be estimated using mixed model repeated measures (MMRM) analysis. The model will use restricted maximum likelihood (REML) with treatment, cycle and treatment-by-cycle interaction as fixed effects, tumor load at baseline as a covariate, and patient as random effect. An unstructured covariance structure will be used to model the within-patient errors.

If this analysis fails to converge, the following covariance structures will be tested in order:

- toeplitz with heterogeneity
- autoregressive with heterogeneity
- compound symmetry with heterogeneous variances
- toeplitz,
- autoregressive
- compound symmetry without heterogeneous variances

The first covariance structure that converges will be used. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. Significance tests will be based on least-squares mean (LSMean) using Type III sum of squares.

2) The ratio of observed $C_{trough,SC}/C_{trough,IV}$ during Cycle 4 will be estimated using the same ANCOVA model as primary analysis.

3) Include patients with all available observed C_{trough} during cycle 7.

4.4.2 Pharmacokinetic Secondary Endpoint

The secondary PK endpoint is the ratio of observed rituximab area under the serum concentration curve of Cycle 7 (AUC_{SC}/AUC_{IV}). A two-sided 90% CI will be constructed. The ratio of AUC will be analyzed in a similar model as described in section 4.4.1.

Individual and mean serum rituximab concentration versus time data will be tabulated and plotted by treatment arms. The serum pharmacokinetics of rituximab will be characterized by estimating observed AUC, observed C_{trough}, observed Cmax, total clearance, volume of distribution at steady state, and terminal half-life (as appropriate for data collected) using noncompartmental analysis (NCA). Estimates for these PK parameters will be tabulated and summarized by treatment group (arithmetic mean, standard deviation (SD), percent arithmetic mean CV%, geometric mean, percent geometric mean coefficient of variation (CV% geo mean), median, minimum, and maximum). Inter-patient variability will be evaluated.

4.5 EFFICACY ANALYSIS

4.5.1 Key Efficacy Endpoint

The key efficacy endpoint is the complete response rate (CRR) at the end of treatment assessment as determined by the IRC using Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014).

Complete response rate (CRR): A complete response is defined as determined by the IRC using Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014). Patients not meeting these criteria, including patients without any post-baseline tumor assessments, will be considered non-responders. And the end of treatment response is defined as the response after the end of treatment or at treatment discontinuation and before any new anti-lymphoma treatment whichever is earlier.

CRR at the end of treatment will be analyzed in frequency tables, including 95% two-sided CIs (Pearson-Clopper) by treatment group. For the difference in response rates, 95% two-sided CIs (Hauck-Andersen) will be calculated. If applicable, the Chi- squared test will be used to compare the CRR between groups. Odds ratio and 95% CI (Wald) will also be calculated by logistic regression.

The rates with 95% CI (Pearson-Clopper) for each response category (CR, PR, PD, SD, NE, Missing) will also be summarized by treatment group.

4.5.2 Secondary Efficacy Endpoints

CRR (CR, CRu) at the end of study treatment, as determined by IRC using International Working Group (IWG) Response Criteria for NHL 1999 Guidelines and CRR at the end of study treatment as determined by the investigator using Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014) will be performed using the same methods as key efficacy endpoint.

Objective response rate (ORR): An objective response is defined as either a CR or PR, as determined by investigators using Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014). Patients not meeting these criteria, including patients without any post-baseline tumor assessments, will be considered non-responders.

ORR at the end of treatment will be analyzed in frequency tables, including 95% two-sided CIs (Pearson-Clopper) by treatment group. For the difference in response rates, 95% two-sided CIs (Hauck-Andersen) will be calculated. If applicable, the Chi- squared test will be used to compare the CRR between groups. Odds ratio and 95% CI (Wald) will also be calculated by logistic regression.

The rates with 95% CI (Pearson-Clopper) for each response category (CR, PR, PD, SD, NE, Missing) will also be summarized by treatment group.

Analyses on ORR assessed by IRC will also be performed using the same methods as ORR assessed by the investigators.

4.5.3 Sensitivity Analyses

As a sensitivity analysis, the response rate will be compared between treatment arms using the stratified Cochran-Mantel-Haenszel test. And the Odds ratio and 95% CI will

also be estimated using a logistic regression stratified by randomization stratification factor IPI Score according to IXRS data.

4.5.4 Subgroup Analyses

To assess the consistency of treatment benefit with respect to the primary efficacy endpoint, CRR, across important subgroups, forest plots (including estimated Odds ratios) will be provided for the following variables:

- Age-group (<65, >=65 years),
- Sex (Male, Female),
- IPI Score (0-2, 3-5),
- ECOG Performance Status (0,>=1)
- BSA: the cut-off will be the 33rd and 66th percentiles of BSA values at baseline: Low (≤ 33rd percentiles); medium (33rd percentiles< BSA ≤ 66th percentiles); high (> 66th percentiles)

4.6 SAFETY ANALYSES

Safety will be assessed through summaries of exposure to study treatment, adverse events, changes in laboratory test results, and changes in vital signs and ECGs. Safety population will be used in all safety analysis.

4.6.1 Exposure of Study Medication

The numbers of patients who experience any dose modification of the study treatment and the reason will be summarized by treatment arm. Descriptive statistics will be presented for treatment duration, total cumulative dose, percentage dose intensity, number of cycles, and number of patients at each treatment cycle.

4.6.2 Adverse Events

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v5.0.

All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest, adverse events leading to study treatment discontinuation, adverse events leading to study discontinuation, adverse event leading to dose modification/interruption, related serious adverse event, Grade 3-5 adverse events (Grade 3, 4, or 5) that occur on or after the first dose of study treatment (i.e., treatment emergent adverse events) will be summarized by mapped term, appropriate thesaurus level, and severity grade. For events of varying severity, the highest grade will be used in the summaries.

Deaths and causes of death reported during the study treatment period and those reported during the follow-up period after treatment completion/discontinuation will be summarized by treatment arm.

4.6.3 Laboratory Data

Clinical laboratory tests will be performed at local laboratories. Laboratory test result data will be summarized over time with inclusion of change from baseline by treatment group. Values outside normal ranges will be summarized. Additionally, a shift table of selected laboratory tests will be used to summarize the baseline and maximum post-baseline severity grade.

4.6.4 Vital Signs

Actual value and change from baseline in vital signs (pulse rate, respiratory rate, blood pressure, pulse oximetry, and temperature) will be summarized over time by the treatment group. Changes in Vital signs (outside normal limits) will be summarized by the treatment group. Baseline is defined as the measurement obtained on Cycle 1, Day 1 prior to first dose of study drug.

4.6.5 ECG Evaluations

Changes in ECG (outside normal limits) will be summarized by the treatment group. Baseline is defined as the measurement obtained on Cycle 1, Day 1 prior to first dose of study drug.

4.6.6 Immunogenicity Analyses

The numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after drug administration (postbaseline incidence) will be summarized by treatment group. When determining postbaseline incidence, patients are considered to be ADA positive if they are ADA negative or have missing data at baseline but develop an ADA response following study drug exposure (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more postbaseline samples is at least 0.60 titer unit greater than the titer of the baseline sample (treatment-enhanced ADA response). Patients are considered to be ADA negative if they are ADA negative or have missing data at baseline and all postbaseline samples are negative, or if they are ADA positive at baseline but do not have any postbaseline samples with a titer that is at least 0.60 titer unit greater than the titer of the baseline sample (treatment unaffected).

The relationship between ADA status and safety, efficacy, and PK endpoints may be analyzed and reported via descriptive statistics.

4.7 MISSING DATA

No values will be imputed for missing data. For CRR/ORR, patients without any post-baseline assessment will be considered as non-responders.

4.8 INTERIM ANALYSES

No efficacy interim analyses are planned.

5. REFERENCES

Final Clinical Study Report - Protocol BO22334 (SABRINA): A Two-stage Phase III, International, Multi-Center, Randomized, Controlled, Open-label Study to Investigate the Pharmacokinetics, Efficacy and Safety of Rituximab SC in Combination With CHOP or CVP Versus Rituximab IV in Combination with CHOP or CVP in Patients With Previously

Appendix 1 Protocol Synopsis	
TITLE:	**A PHASE II COMPARATIVE, OPEN LABEL, RANDOMIZED, MULTICENTER, CHINA-ONLY STUDY TO INVESTIGATE THE PHARMACOKINETICS, EFFICACY AND SAFETY OF SUBCUTANEOUS RITUXIMAB VERSUS INTRAVENOUS RITUXIMAB, BOTH IN COMBINATION WITH CHOP IN PREVIOUSLY UNTREATED PATIENTS WITH CD20 POSITIVE DIFFUSE LARGE B CELL LYMPHOMA**
PROTOCOL NUMBER:	YO42207
VERSION NUMBER:	1.0
IND NUMBER:	To be determined
TEST PRODUCT:	Rituximab (RO0452294) (MabThera→)
PHASE:	II
INDICATION:	Previously untreated CD20 positive Diffuse Large B Cell Lymphoma
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the efficacy, safety, and pharmacokinetics (PK) of subcutaneous (SC) rituximab compared with intravenous (IV) rituximab, both in combination with cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP), in previously untreated patients with CD20 positive diffuse large B cell lymphoma (DLBCL). Specific objectives and corresponding endpoints for the study are outlined below.

Primary Objectives

The primary objective of this study is to demonstrate the non-inferiority of rituximab serum C_{trough} obtained at Cycle 7, 21 days after SC administration, with that obtained at Cycle 7, 21 days after IV administration on the basis of the following endpoint:

- Ratio of $C_{trough,SC}/C_{trough,IV}$ during Cycle 7

Secondary Objectives

The secondary objectives of this study are to compare and assess other PK parameters, efficacy and safety profiles (including immunogenicity) of rituximab SC and rituximab IV, both in combination with CHOP, on the basis of the following endpoints and outcome measures:

- Ratio of AUC_{SC}/AUC_{IV} during Cycle 7
- Other PK parameters, such as AUC and C_{trough} at other treatment cycles, maximum serum concentration (C_{max}), total clearance, volume of distribution at steady state, and terminal half-life ($t_{1/2}$) (if feasible or appropriate) as appropriate
- Complete response rate (CRR) at the end of the study treatment, as determined by the Independent Review Committee (IRC) using Lugano Response Criteria for Malignant Lymphoma as key efficacy endpoint
- Objective response rate (ORR), defined as complete response (CR) or partial response (PR) at the end of the study treatment, as determined by investigator and IRC using Lugano Response Criteria for Malignant Lymphoma
- CRR (CR, complete response unconfirmed [CRu]) at the end of study treatment, as determined by IRC using International Working Group (IWG) Response Criteria for Non-Hodgkin's lymphoma (NHL) 1999 Guidelines
- CRR at the end of the study treatment, as determined by the investigator using Lugano Response Criteria for Malignant Lymphoma
- Safety outcomes as assessed by adverse events, including rituximab administration-related reactions (ARRs), laboratory assessments, and vital signs; and immunogenicity as assessed by anti-rituximab antibodies and anti-rHuPH20 antibodies

Study Design

Description of Study

This is a Phase II, multicenter, randomized, controlled, open-label, China-only study to investigate the PK, efficacy, and safety of rituximab SC in combination with CHOP versus rituximab IV in combination with CHOP in previously untreated patients with CD20 positive DLBCL. This study will be conducted at approximately 8 sites in China. Approximately 50 patients will receive eight cycles of rituximab SC or rituximab IV combined with six or eight cycles of standard CHOP chemotherapy. Centers must choose whether they plan to administer six or eight cycles of CHOP chemotherapy prior to study start. Previous results have demonstrated that a fixed rituximab SC dose at 1400 mg is expected to achieve non-inferior C_{trough} values to the rituximab IV regimen (375 mg/m^2) prior to Cycle 8 (Study BO22334). In this study, a sample size of 50 patients (approximately 18 evaluable patients per arm) who have completed Cycle 7 will be adequate for testing non-inferiority for the estimated ratio $C_{trough,SC}/C_{trough,IV}$. Previously untreated patients with CD20 positive DLBCL will be randomized into the following two treatment groups at a 1:1 ratio (crossover to the experimental arm is not permitted):

- R^{SC}-CHOP: Cycle 1 rituximab IV plus seven cycles of rituximab SC in combination with six or eight cycles of CHOP chemotherapy administered every 3 weeks; rituximab IV will be used at the standard dose of 375 mg/m^2 and rituximab SC will be given at a dose of 1400 mg as confirmed in the Phase III Study BO22334.
- R^{IV}-CHOP: eight cycles of rituximab IV in combination with six or eight cycles of CHOP chemotherapy administered every 3 weeks; rituximab IV will be used at the standard dose of 375 mg/m^2.

Eligible patients will be stratified during randomization according to International Prognostic Index (IPI) scores (IPI 0-2 versus IPI 3–5).

Patients will be assessed for disease response by the investigator and IRC, on the basis of regular clinical and laboratory examinations, physical examinations, computed tomography (CT) scans, positron emission tomography (PET)-CT scans, and bone marrow examinations, according to

the Lugano Response Criteria for Malignant Lymphoma. PET-CT and dedicated CT scans will be obtained at screening and 6-8 weeks after completion of study treatment, or sooner in the event that a patient discontinues early. An interim assessment will be obtained after Cycle 4 and should include PET-CT and dedicated CT. If local practice prohibits obtaining both assessments after Cycle 4, PET-CT alone (preferred) or CT alone may be obtained at this time point. During the follow-up period, imaging (may be CT only) will be performed every 3 months, i.e., Week 12 and 24 after last treatment, in accordance with study visits and will include the neck (if involved at baseline), chest, abdomen, and pelvis.

After the end of study treatment, patients will be followed-up every 3 months for 6 months (i.e., 12 and 24 weeks after the last dose of study treatment). Assessments will include clinical evaluation of tumor response/progression, PK and immunogenicity (blood sampling), physical examination, standard hematologic and biochemistry assessments, vital signs and weight measurements, liver and spleen size and B-symptoms assessments.

Safety will be evaluated by monitoring all adverse events, and abnormalities identified through physical examination, vital signs, and laboratory assessments. Such events will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5 (NCI CTCAE v5.0). Laboratory safety assessments will include the routine monitoring of hematology and blood chemistries.

Number of Patients

Approximately 50 patients with previously untreated CD20 positive DLBCL will be enrolled in this study.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Able and willing to provide written informed consent and to comply with the study protocol
- Age ≥18 and ≤80 years at time of signing Informed Consent Form
- Previously untreated CD20 positive DLBCL histologically documented
- Patients with an IPI score of 1 to 5 or IPI score of 0 with bulky disease, defined as one lesion ≥7.5 cm
- At least one bi-dimensionally measurable lesion defined as ≥1.5 cm in its largest dimension on CT scan
- Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2
- Left ventricular ejection fraction (LVEF) ≥50% on cardiac multiple-gated acquisition (MUGA) scan or cardiac echocardiogram
- A negative serum pregnancy test or a negative urine pregnancy test within 7 days prior to study treatment must be available both for pre-menopausal women (including those who have had a tubal ligation) and for women who are less than 2 years after the onset of menopause; if negative serum pregnancy test is within 14 days of study treatment start, a confirmatory urine pregnancy test must be available within 7 days prior to study treatment start
- For men who are not surgically sterile, agreement to use a barrier method of contraception during the treatment period and until ≥12 months after the last dose of rituximab SC or rituximab IV or according to institutional guidelines for CHOP chemotherapy, whichever is longer, and agreement to request that their partners use an additional method of contraception, such as oral contraceptives, intrauterine device, barrier method, or spermicidal jelly

- For women of reproductive potential who are not surgically sterile, agreement to use adequate methods of contraception, such as oral contraceptives, intrauterine device, or barrier method of contraception in conjunction with spermicidal jelly during the treatment period and until ≥12 months after the last dose of rituximab SC or rituximab IV or according to institutional guidelines for CHOP chemotherapy, whichever is longer
- Adequate hematologic function confirmed within 14 days prior to randomization which is independent to stimulating factors and transfusion (unless related to lymphoma infiltration of the bone marrow)
    - Hemoglobin ≥9.0 g/dL
    - Absolute neutrophil count (ANC) ≥1.5 · 10^9/L
    - Platelet count ≥75 · 10^9/L

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Transformed NHL or types of NHL other than DLBCL and its subtypes according to World Health Organization classification
- History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies or known sensitivity or allergy to murine products
- Contraindication to any of the individual components of CHOP, including prior receipt of anthracyclines
- Prior therapy for DLBCL, with the exception of nodal biopsy or local irradiation or surgery for diagnosis
- Prior treatment with cytotoxic drugs or rituximab for another condition (e.g., rheumatoid arthritis) or prior use of an anti-CD20 antibody
- Current or recent (within the 30 days prior to starting study treatment) treatment with another investigational drug or participation in another investigational therapeutic study
- Ongoing corticosteroid use, >30 mg/day of prednisone or equivalent
    - Patients receiving corticosteroid treatment with ≤30 mg/day of prednisone or equivalent must be documented to be on a stable dose for duration of at least 4 weeks prior to randomization.
- Primary central nervous system (CNS) lymphoma, blastic variant of mantle cell lymphoma, or histologic evidence of transformation to a Burkitt lymphoma, primary mediastinal DLBCL, primary effusion lymphoma, and primary cutaneous DLBCL
- History of other malignancy that could affect compliance with the protocol or interpretation of results
    - Patients with a history of curatively treated basal or squamous cell carcinoma or melanoma of the skin or in situ carcinoma of the cervix are eligible.
    - Patients with a malignancy that has been treated but not with curative intent will also be excluded unless the malignancy has been in remission without treatment for ≥5 years prior to enrollment.

- Evidence of significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results, including but not limited to significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina) or pulmonary disease (including obstructive pulmonary disease and history of bronchospasm)
- Any of the following abnormal laboratory values:
  - Creatinine >1.5 · upper limit of normal (ULN) (unless creatinine clearance normal) or calculated creatinine clearance <40 mL/min (using the Cockcroft-Gault formula)
  - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5 · ULN
  - Total bilirubin ≥1.5 · ULN; patients with documented Gilbert disease may be enrolled if total bilirubin is ≤3.0 · ULN
  - International normalized ratio (INR) ≥1.5 · ULN in the absence of therapeutic anticoagulation
  - Partial thromboplastin time (PTT) or activated Partial thromboplastin time (aPTT) >1.5 · ULN in the absence of a lupus anticoagulant
- Positive test results for chronic hepatitis B virus (HBV) infection (defined as positive hepatitis B surface antigen [HBsAg] serology)
  - Patients with occult or prior HBV infection (defined as negative HBsAg and positive total hepatitis B core antibody [HBcAb]) may be included if HBV DNA is undetectable, provided that they are willing to undergo monthly DNA testing during the treatment period and the follow-up period.
- Positive test results for hepatitis C (hepatitis C virus [HCV] antibody serology testing)
  - Patients positive for HCV antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.
- Known history of human immunodeficiency virus (HIV) seropositive status or infection
- Signs or symptoms of other active and/or severe infection
- Evidence of any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates use of an investigational drug or patient at high risk from treatment complications
- Any co-existing medical or psychological condition that would compromise ability to give informed consent

End of Study and Length of Study

The end of study is defined as the date when the last patient last visit (LPLV) occurs. LPLV is expected to occur approximately 6 months after the last patient enrolled has received the last study treatment, or sooner, if all patients have progressed, died, or withdrawn from the study. The Sponsor has the right to terminate the study at any time.

Investigational Medicinal Products

Test Product (Investigational Drug)

The experimental investigational medicinal product of the study is rituximab SC supplied as a ready-to-use liquid formulation with a nominal content of 120 mg/mL rituximab. The drug product contains 2000 U/mL rHuPH20 acting as a permeation enhancer, histidine/histidine-HCl

(buffer), α,α-trehalose (bulking agent), methionine (stabilizer), and polysorbate 80 (surfactant) in Water for Injection (WFI) at a pH of 5.5. Rituximab SC will be administered by SC injection on Day 1 of Cycles 2 to 8 to patients randomized to the R^{SC}-CHOP treatment arm.

Comparator

The comparator investigational medicinal product of the study is rituximab IV provided as 500 mg/50 mL liquid-filled vials with a nominal content of 10 mg/mL rituximab. The drug product contains sodium acetate (buffer), sodium chloride (tonicity adjustment), and polysorbate 80 (surfactant) in WFI at a pH of 6.5. Rituximab IV will be administered by IV infusion on Day 1 of Cycles 1 to 8 to patients randomized to the R^{IV}-CHOP treatment arm and on Day 1 of Cycle 1 to patients randomized to R^{SC}-CHOP treatment arm.

Non-Investigational Medicinal Products

The CHOP chemotherapy will be prepared according to the standard practice at the institution.

Statistical Methods

Primary Analysis

All PK analyses will be based on all patients for whom PK assessments were made. PK analyses will be analyzed as treated. Patients will be excluded from the PK analysis population if they significantly violate the inclusion or exclusion criteria, deviate significantly from the protocol, or if data are unavailable or incomplete, where the PK analysis might be influenced. Excluded cases will be documented, including the reason for exclusion. All decisions on exclusions from the analysis will be made prior to database closure.

The primary PK endpoint is the ratio of $C_{trough,SC}/C_{trough,IV}$ during Cycle 7. The serum rituximab C_{trough} at Cycle 7 will be measured at pre-dose of Cycle 8. The lower limit of the two-sided 90% confidence interval (CI) should be above 0.80 in order to show non-inferiority of $C_{trough,SC}$ versus $C_{trough,IV}$.

Determination of Sample Size

Under the assumption of a coefficient of variation equal to 0.5 and assuming that the true C_{trough} of rituximab SC formulation is 20% above the rituximab IV formulation (i.e., mean $C_{trough,SC}$ to be 20% above $C_{trough,IV}$), 20 patients in each treatment arm are needed in order to achieve 80% power with one-sided alpha of 0.05 (i.e., 2-sided 90% confidence interval [CI]). Assuming that 20% of patients would not have valid PK data at Cycle 8 pre-dose, a total of approximately 50 patients will be enrolled into the study.

Appendix 2
Schedule of Activities

Assessment/Procedure	Screening		Treatment Period				End of Treatment		Follow-Up (6 months)
			C1–3	C4		C5–8	TCV	ETTV [a]	
	Days −28 to −1	Days −14 to −1	D1	D1	Interim Assessment D19 (±3)	D1	6–8 weeks after last treatment	4–8 weeks after last treatment	12 weeks and 24 weeks after last treatment
Written informed consent [b]	x								
Inclusion/exclusion criteria	x								
Demographic information and medical history		x							
Height		x							
BSA		x							
Weight		x	x	x		x	x	x	x
Vital Signs		x	x	x		x	x	x	x
Complete physical exam [c]	x								
Targeted physical exam [d]			x	x	x	x	x	x	x
ECOG performance status [e]		x	x	x		x			x
DLBCL diagnosis, staging, and IPI score [f]	x								
B symptoms		x	x	x		x	x	x	x
Tumor assessment [g]	x				x		x	x	x
12-lead-ECG and LVEF	x						x	x	x

Hematology and serum chemistry [h]		x	x	x	x	x	x	x	x
Coagulation (aPTT or PTT, PT, and INR)		x							
Pregnancy test (if applicable) [i]		x							x
Serology testing for HCV, HBV [j]		x							
Hepatitis B DNA on PCR (as indicated) [k]		x	x	x		x	x	x	x
Lumbar puncture for CSF (as indicated) [l]	x								
Bone marrow aspirate + biopsy (as indicated) [m]	x						x	x	
Study treatment [n]			x	x		x			
Rituximab PK sample [o]			x	x		x		x	x [p]
Anti-rHuPH20 antibody sample [q]			x[r]	x[r]		x[r]		x	x [s]
Anti-rituximab antibody sample			x[r]	x[r]		x[r]		x	x [s]
Sample for quantitative immunoglobulins (IgA, IgG, and IgM)		x						x	x
Adverse events [t]	x	x	x	x	x	x	x	x	x
Concomitant medications [u]	x	x	x	x	x	x	x	x	x

BSA = body surface area; C = cycle; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; CSF = cerebrospinal fluid; D = day; DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; ETTV = early treatment termination visit, FACS = fluorescence-activated cell sorting; HBV = hepatitis B virus; HCV = hepatitis C virus; IPI = International Prognostic Index; IV = intravenous; LVEF = left ventricular ejection fraction; TCV = treatment completion visit, SC = subcutaneous.

Note: After the end of the study treatment period, all patients will be followed until the end of the study according to local practice for resolution of adverse events related to rituximab therapy, survival, disease status, and whether a new lymphoma treatment has been started. The visit window during each cycle of study treatment is ±3 days. The window for the treatment discontinuation/early treatment termination and post-treatment study visits is ± 1 week (unless otherwise specified).

[a] Patients who discontinue the study treatment prematurely are required to return to the clinic for an early termination visit within 4–8 weeks after the last dose of study treatment.

[b] Written informed consent must be obtained prior to any study-specific procedures (including screening evaluations) performed or any prohibited medications being withheld for purposes of study participation. Please see Section 4.5.1 for more details.

[c] Includes evaluation of the head, eyes, ears, nose, and throat, and cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems. See Section 4.5.3 for more details.

[d] A targeted physical examination should be limited to systems of primary relevance, including cardiovascular, respiratory, those associated with symptoms, and those with tumor assessment (lymph nodes, liver, and spleen).

[e] ECOG performance status must be ≤2 for inclusion of the patient into the study.

[f] Diagnosis of DLBCL before treatment must have included histological diagnosis and initial CD20 expression confirmation. See Section 4.1.1 for more details.

[g] Tumor assessments will be based on PET-CT scans (or MRI scans, if CT scans are contraindicated) of the neck (if clinically indicated), chest, abdomen, and pelvis where applicable. PET-CT scans will be obtained at screening, interim response assessment (i.e., Day 19 [±3 days] of Cycle 4) and End of Treatment assessment (6–8 weeks after the last dose of study treatment or 4–8 weeks after last dose of study treatment for early discontinuation). All other imaging may be CT only (i.e., follow-up period [12 and 24 weeks after the last dose of study treatment]).

[h] Hematology will include hemoglobin, hematocrit, platelet count, RBC count, WBC count, percent or absolute differential count. At screening, serum chemistry will include sodium, potassium, chloride, bicarbonate, BUN, creatinine, calcium, phosphorus, total bilirubin, total protein, albumin, AST, ALT, LDH, alkaline phosphatase, uric acid, and calculated creatinine clearance. During Cycles 1–8 and the follow-up period, serum chemistry will include sodium, potassium, creatinine, calcium, total bilirubin, total protein, albumin, AST, ALT, LDH, alkaline phosphatase, and uric acid.

[i] A negative serum pregnancy test or a negative urine pregnancy test within 7 days prior to study treatment must be available both for pre-menopausal women (including those who have had a tubal ligation) and for women who are less than 2 years after the onset of menopause; if a negative serum test within 14 days prior to study treatment, a confirmatory urine pregnancy test must be within 1 week prior to study treatment start.

[j] Patients known to have HIV, hepatitis C, active hepatitis B, or signs or symptoms of other active and/or severe infection must not be included in the study. Serology should be performed according to clinical judgment before and during treatment with rituximab. Patients found to have HIV, hepatitis C, or active hepatitis B must either not start or must stop rituximab therapy and enter active follow-up. Local guidelines for patient consent to viral testing must be adhered to.

[k] Patients with occult or prior HBV infection may be included if HBV DNA is undetectable, provided that they are willing to undergo monthly DNA testing.

[l] Lumbar puncture is indicated for patients with high-risk disease or with one or more of the following sites of involvement: paranasal sinuses, testicular, paramenigeal, peri-orbital, CNS, paravertebral, or bone marrow.

[m] Bone marrow examinations are required at screening and should include biopsy for morphology. Repeat bone marrow examinations are required if the bone marrow was involved with tumor at screening and the repeat bone marrow examination is required to confirm a radiological assessment of complete response at the end of therapy.

[n] See details on administration schedule of the study treatment in Section 4.3.2.

[o] See details on rituximab PK sample in Appendix 2.

[p] Samples for rituximab PK will be collected 24 weeks after last rituximab administration.

[q] Only patients who are randomized to rituximab SC will be assessed for anti-rHuPH20 antibodies.

[r] Samples are drawn within 2 hours pre-dose.

[s] Samples for anti-rituximab antibodies and anti-rHuPH20 antibodies will be collected 12 weeks and 24 weeks after last rituximab dose.[t] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 28 days after the final dose of study drug. After this

period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment (see Section 5.6).

[u] Any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 28 days prior to initiation of study drug to study termination. Any new lymphoma treatment initiated after the baseline visit will be recorded as concomitant treatments.

Signature Page for SAP YO42207 Rituximab v1
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Approval Task	[redacted] Company Signatory 20-May-2022 08:16:18 GMT+0000