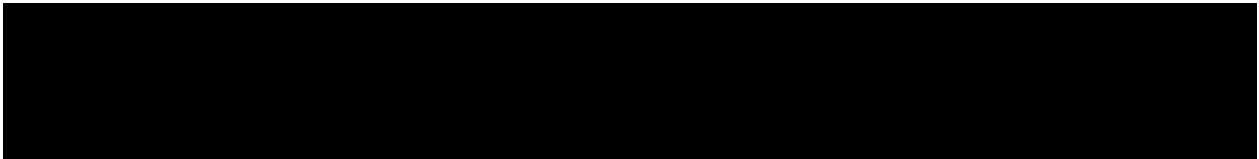




**A PHASE 3, RANDOMIZED, DOUBLE-BLIND STUDY OF
PF-05280586 VERSUS RITUXIMAB FOR THE FIRST-LINE TREATMENT OF
PATIENTS WITH CD20-POSITIVE, LOW TUMOR BURDEN, FOLLICULAR
LYMPHOMA**

Compound:	PF-05280586
Compound Name:	Not Applicable
US IND Number:	110,426
European Clinical Trial Database (EudraCT) Number:	2014-000132-41
Protocol Number:	B3281006
Phase:	3



Document History

Document	Version Date	Summary of Changes and Rationale
Original Protocol	14 February 2014	Not Applicable
Amendment 1	08 May 2014	<ul style="list-style-type: none"> • Added the CD-19 B-cell results from the Phase 1/2 PF-05280586 study to the Protocol Summary and Section 1.2.2. • Added text in the Protocol Summary, Section 1.1 and Section 3 to clarify the definition of low tumor burden used to enroll patients in the study. • Updated the Protocol Summary and Section 4.1 to indicate that normal LDH will be required at Screening for inclusion. • Updated the Schedule of Assessments to indicate that LDH and β-2 microglobulin will be collected throughout the study for increased safety monitoring. • Updated the Schedule of Assessments, Section 6 and Section 7 to indicate that Immunogenicity (ADA/Nab) samples will be collected at Day 15 to provide more information regarding the onset of any ADA/Nab findings. Removed Day 22 Immunogenicity sampling. Made additional updates to clarify sample collection requirements for ADA/Nab, to remove references to cross-reactivity testing as it will not be conducted in this study, and to clarify that additional follow-up will not be required for patients with positive ADA/Nab samples. • Updated footnotes in the Schedule of Assessments, Section 6 and Section 7 to indicate that all Physical Examinations must include a thorough assessment of the lymph nodes, liver, and spleen to ensure adequate safety monitoring. • Updated a footnote in the Schedule of

		<p>Assessments, Section 6 and Section 7 to clarify that HIV testing is required at Screening unless prohibited by local regulations.</p> <ul style="list-style-type: none">• Updated additional footnotes in the Schedule of assessments to ensure that they are consistent with the rest of the protocol and to correct minor errors.• Moved the description of the results of the completed Phase 1/2 PF-05280586 study from Section 1 to Section 1.2.2.• Changed the title of Section 1.2.1.1 to clarify that it discusses the efficacy of rituximab monotherapy in low tumor burden follicular lymphoma.• Removed the text in Section 3 that describes the ISRC functioning as an advisory group as the ISRC will meet on an ad hoc basis if required.• Updated Section 4.1 to indicate that both male and female patients of childbearing potential must agree to use contraception.• Updated Section 4.2 to indicate that patients with $\geq 5000/\text{mm}^3$ circulating lymphoma cells at Screening will be excluded to avoid patients with bone marrow involvement.• Updated Section 4.2 to indicate that patients with a body surface area of >3 will be excluded from the study.• Removed male and female condoms with spermicide from the list of highly effective methods of contraception in Section 4.4 as requested by regulators.• Updated Section 5.1 to refer to patients rather than subjects to ensure consistency with the rest of the protocol.
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		<ul style="list-style-type: none"> • Additional updates to Section 8 and Section 15 to assure consistency with the standard language in Pfizer’s current protocol template. • Renumbered references to match the order in which they appear in the current protocol. • Corrected typographical errors and made minor updates to the text for clarity throughout the document.
Amendment 2	05 September 2014	<ul style="list-style-type: none"> • For Japan only: Added an additional analysis to test whether the difference between the ORR of rituximab-Pfizer and rituximab-EU is between a margin of -14.9% to 14.9% according to a requirement from the regulatory authority in Japan.
Amendment 3	04 December 2014	<ul style="list-style-type: none"> • Testing for circulating lymphoma cells at Screening added to the Schedule of Assessments and Section 6.1. • Contraception check added to Schedule of Assessments. • Updated information from the Ardeshta et al. study in the Protocol Summary and Section 9.1 to include data reported in Lancet Oncology in 2014. Previous data were from a 2010 abstract. • Deleted ADR table in Section 1.2.1.2 for MabThera and instead referenced the MabThera SPC to avoid any inconsistencies. • Updated Section 4.1, Inclusion Criterion 1 to align with global requirements for age of consent. • Updated Section 4.1, Inclusion Criterion 2 and Section 6.1 to require that patients diagnosed with fine needle aspiration cytology or a biopsy from non-lymphoid tissue will be required to have an excisional

		<p>or core needle tumor tissue biopsy from a lymph node to determine eligibility (unless eligibility can be confirmed by the central pathology reviewer prior to randomization).</p> <ul style="list-style-type: none">• Updated Section 4.1, Inclusion Criterion 6 to clarify the requirement for no <u>clinically</u> significant serous effusions.• Updated Section 4.2, Exclusion Criterion 9 to exclude patients with any history of allergy or hypersensitivity to murine, chimeric, humanized, or human monoclonal antibody treatments.• Updated Section 4.2, Exclusion Criterion 13 to provide clarity around exclusion of patients with positive tests for HBsAg, HBcAb, or HCVAb.• Updated Section 4.2, Exclusion Criterion 14 to include broad antimicrobial treatment, as opposed to antibiotics.• Updated Section 4.2, Exclusion Criterion 15 to clarify the exception to history of cancer in the last 5 years only applies to non-melanoma skin tumors, in situ cervical carcinoma, or in situ breast cancer treated with curative intent with no history of metastatic disease.• Section 4.3 updated to allow patients to be randomized within 5 business days of Day 1 to accommodate IP shipment from central pharmacies to sites.• Sections 5.1 and 6.2.1 updated to include a requirement to complete an Eligibility Review Form and send to the Sponsor for approval prior to randomization.• Section 5.3.2 updated to allow IP preparation utilizing either the approved MabThera SPC or the local product label for rituximab.• Section 5.3.2.1 updated to align with the
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		<p>MabThera SPC by allowing for dilution concentrations of 1 mg/mL to 4 mg/mL.</p> <ul style="list-style-type: none">• Updated Section 5.3.3 to provide clarity on the BSA calculation requirements.• Updated Section 5.3.3 to provide guidance on post-infusion observation of patients.• Updated Section 5.5 to prohibit long term high dose steroid use.• Updated Section 5.5 to prohibit administration of vaccines containing live viruses during the study.• Updated Schedule of Assessments and Section 6.1 to extend the screening window to 56 days with exception of Screening labs, which must be performed within 28 days of Day 1.• Updated section 6.2.2 and 6.2.3 to clarify that the end of the infusion is the time when the entire dose of study medication has been administered and the 10 minute flush with diluent has been completed.• Updated Sections 6.2.2, 6.2.3, 6.2.4 and the Schedule of Assessments to include assessment of follicular lymphoma signs and symptoms, including lymphoma-related B symptoms, throughout the study.• Updated Schedule of Assessments and Sections 6.2.3 and 6.2.4 to clarify that the follow-up PET and bone marrow biopsy should be performed within 4 weeks of a contrast-enhanced CT in which the patient achieves a complete remission.• Updated section 6.3 to clarify that patients who cannot received all four doses of study medication may be withdrawn from treatment, but may remain in the study
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		<ul style="list-style-type: none">• Updated Section 7.1 and added Appendix 3 to provide guidance that Investigators should utilize the revised response criteria for malignant lymphoma (2007) for determining complete remission.• Coagulation testing at Screening and End of Study was removed from the Schedule of Assessments, Sections 6.1 and 6.2.4, and Section 7.2.4.• Updated Section 7.2.4 to clarify which laboratory tests will be performed centrally and which will be performed locally.• Updated Section 7.2.4 to clarify that a single retest for an exclusionary laboratory value may be conducted during Screening.• Updated Section 7.5 to correct an error that indicated that WBCs must be collected to assess CD19 B cell counts.• Updated Section 7.6 to clarify eligibility for randomization based on local histopathology review and availability of archival tissue.• Banked biospecimen sample collection was removed from the Schedule of Assessments and Section 7.7 deleted.• Updated Section 8.7 to reference CTCAE V4.03 instead of listing the specific intensities. Additionally, NCI CTCAE severity grades for infusion related reactions were added.• Changed “subject” to “patient” to ensure consistency throughout the document.• Changed “IVRS” to “IMPALA” throughout the document. <p>Corrected typographical errors</p>
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<p>Amendment 4</p>	<p>19 April 2016</p>	<ul style="list-style-type: none"> • Changed “central radiology review” to “central review” as the central assessment of response also involves clinical data, including the development of B symptoms and bone marrow biopsy results. Sections impacted: Protocol Summary, Section 2.2.1, Section 9.3.2.2 and Section 9.3.2.3. • Revised protocol to allow patients with LDH values of up to 1.5 the upper limit of normal to enroll in the study. Sections impacted: Protocol Summary, Section 1.1, Section 3, and Section 4.1. • Clarified that sites may perform either a diagnostic quality PET/CT or a separate CT scan at visits where imaging is required (Screening, Week 13, Week 26, Week 39, and Week 52). Also clarified that PET/CT scans should encompass the base of the skull to the proximal femurs and provided additional guidance on imaging requirements for patients who cannot receive IV contrast. Sections impacted: Schedule of Assessments, Section 6.1, Section 6.2.3, Section 6.2.4, and Section 7.1. • Expanded visit window from 7 days to 14 days for Visits 7, 8, 9, and 10. Sections impacted: Schedule of Assessments. • Clarified the vital signs which should be collected every 30 minutes during IP infusion (heart rate, seated blood pressure, respiratory rate, and oral or tympanic body temperature) and specified that a ± 5 minute window is acceptable for the collection of vital signs during IP infusion. Sections impacted: Schedule of Assessments, Section 5.3.3 and Section 7.2.2. • Extended the window for patients who have had a previous bone marrow biopsy from 8 weeks to 12 weeks prior to Day 1 and allow patients who have had a positive bone marrow biopsy or aspiration to enter the study without
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		<p>requiring a repeat biopsy or aspiration to confirm marrow involvement. Sections impacted: Schedule of Assessments and Section 6.1.</p> <ul style="list-style-type: none">• Removed the requirement for steroid premedication to be administered 30 minutes prior to the start of IP infusion as appropriate timing of steroid administration will vary depending on the route of administration and premedications may be administered in accordance with the institution’s standard of care. Clarified that changes in pre-medication doses after the first infusion should be made in accordance with standard of care and local rituximab labeling. Sections impacted: Schedule of Assessments and Section 5.3.2.2.• Removed “untreated” from Inclusion Criterion 2 and updated Exclusion Criterion 6 to clarify that patients who have received previous systemic therapy for follicular lymphoma (FL) are not eligible for participation, but patients who have received localized radiotherapy for FL may participate in the study. Sections impacted: Section 4.1 and Section 4.2.• Clarified that either a tissue blocks or slides are acceptable for the retrospective central pathology review. Removed the requirement that patients diagnosed by fine needle aspiration or a biopsy from non-lymphoid tissue undergo central pathology review prior to be enrolled in the study. Section impacted: Schedule of Assessments, Section 4.1, Section 6.1 and Section 7.6.• Revised Inclusion Criterion 5 regarding measurable disease to clarify that lesions must be measurable via imaging and to provide minimum measurements for both nodal and extra-nodal lesions. Sections impacted: Section 4.1 and Section 9.2.2.• Clarified that contraception is required for
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		<p>sexually active patients who are biologically capable of having children and at risk for pregnancy in accordance with the current Pfizer protocol template. Section impacted: Section 4.4.</p> <ul style="list-style-type: none">• Clarified that brain imaging is not required to rule out CNS involvement, but may be conducted if clinically indicated. Section impacted: Section 4.2.• Clarified that patients with any history of T-cell lymphoma are excluded from participation. Section impacted: Section 4.2.• Clarified that an Early Termination Visit is not required for patients who withdraw from the study at a scheduled study visit. Section impacted: Section 6.3.• Corrected the list of required clinical laboratory tests and clarified that local laboratory testing may be used to determine eligibility or monitor safety if it is not feasible to do so using the central laboratory. Section impacted: Section 7.2.4.• Clarified the Per-Protocol Population definition to include all randomized patients who receive at least one dose of treatment and have measurable disease at baseline confirmed by central review. Section impacted: Section 9.2.2.• Clarified the definition of Time to Treatment Failure as time from date of randomization to discontinuation from study for any reason. Section impacted: Section 9.3.2.1.• Corrected “objective tumor response” to “overall response” in the discussion regarding the Duration of Response endpoint. Section impacted: Section 9.3.2.3.• Updated safety reporting text to be consistent with current Pfizer protocol template. Section
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		<p>impacted: Section 8.</p> <ul style="list-style-type: none">• Updated text regarding communication of study results to be consistent with current Pfizer protocol template. Section impacted: Section 15.• Corrected minor typographical errors and clarified abbreviations throughout the document.
<p>This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and institutional review boards/ethics committees (IRBs/ECs).</p>		

PROTOCOL SUMMARY

Background and Rationale:	<p>PF-05280586 (hereafter designated rituximab-Pfizer) is being developed as a potential biosimilar to rituximab. Rituximab is approved for two broad indications: musculoskeletal and connective tissue diseases and B-cell malignancies. Rituximab is an effective therapy for the treatment of patients with CD-20 positive, B-cell malignancies.^{1,2} Rituxan[®] is the commercially available product in the United States and will be referred to as rituximab-US; MabThera is the commercially available product in the European Union and will be referred to as rituximab-EU. In Japan the commercially available product is Rituxan[®].</p> <p>Rituximab is a chimeric monoclonal antibody comprised of a human IgG1_K Fc region and a murine variable region that binds specifically to human CD20. Rituximab contains 2 heavy (H) chains, each comprising 451 amino acids and 2 kappa light (L) chains each comprising of 213 amino acids, which are disulfide-bonded to form a 4-chain molecule (H₂L₂). Rituximab-Pfizer has the same primary amino acid sequence as the commercially available rituximab product.</p> <p>The term “biosimilar” refers to a biologic drug that is developed to be highly similar to an existing licensed reference biologic. Biosimilars are intended to treat the same diseases as the reference biologic using the same dose and treatment regimen. Unlike generic versions of chemically-synthesized small molecule therapies, biosimilars are not structurally identical to their reference biologic. This is due to the purity, characteristics, and activity of a specific biologic being dependent on and sensitive to changes in the process by which it was manufactured. Therefore, the aim is to create a product with no clinically meaningful differences between the biosimilar and the reference biologic in terms of chemistry, manufacturing, and controls (CMC), purity, potency, pharmacokinetics (PK), safety, immunogenicity, and efficacy.</p> <p>The PK of rituximab-Pfizer, rituximab-EU and rituximab-US were compared in a Phase 1/2 study conducted in patients with rheumatoid arthritis (Protocol B3281001). The results showed that the 90% confidence intervals (CIs) for the test-to-reference ratios of the maximum serum concentration (C_{max}), area under the concentration-time curve (AUC) from time zero to the last quantifiable time point (AUC_T), and AUC from time zero extrapolated to infinity (AUC_{0-∞}) were within the pre-specified window of 80.00% to 125.00% for the comparisons of rituximab-Pfizer to rituximab-EU and rituximab-US, and for the</p>
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	<p>comparison of rituximab-EU to rituximab-US, demonstrating the PK similarity of the 3 products. The study results also showed that the safety and immunogenicity profiles and CD-19 positive B-cell reductions were comparable across rituximab-Pfizer, rituximab-EU, and rituximab-US. Because of the similarity between rituximab-US and rituximab-EU, only rituximab-EU will be used as a comparator in the current study.</p> <p>The demonstration of similarity in efficacy between a biosimilar and the innovator product is an essential component of a clinical trial program that collectively provides the evidence of biosimilarity. The current study will evaluate the efficacy, safety, PK, and immunogenicity of rituximab-Pfizer versus rituximab-EU in patients with CD20-positive, low tumor burden follicular lymphoma (LTB-FL) in the first-line treatment setting. While rituximab monotherapy in the first line setting is not an approved indication, it is an acceptable treatment option in low tumor burden follicular lymphoma.^{4,5} Using rituximab monotherapy allows the assessment of biosimilarity without the potentially confounding factors that would be introduced by combining rituximab with chemotherapy in more advanced stage patients; this is particularly important for the evaluation of comparative immunogenicity.</p> <p>Throughout this clinical trial protocol, PF-05280586 is referred to as rituximab-Pfizer; however, biosimilarity has not yet been established and is not claimed. Likewise, the general term rituximab is sometimes used for convenience when discussing the 2 blinded study treatments but is not a claim of biosimilarity. Biosimilarity will be supported by analytical, non-clinical, clinical PK, pharmacodynamic (PD), safety and efficacy studies.</p>
<p>Objectives and Endpoints:</p>	<p>Primary Objective</p> <ul style="list-style-type: none"> • To compare the efficacy of rituximab-Pfizer to rituximab-EU when administered as a first-line treatment to patients with CD20-positive, low tumor burden follicular lymphoma (LTB-FL). <p>Secondary Objectives</p> <ul style="list-style-type: none"> • To evaluate the safety of rituximab-Pfizer and rituximab-EU. • To evaluate the population pharmacokinetics of rituximab-Pfizer and rituximab-EU.

	<ul style="list-style-type: none">• To evaluate the immunogenicity of rituximab-Pfizer and rituximab-EU.• To characterize CD19-positive B-cell depletion and recovery in patients receiving rituximab-Pfizer and rituximab-EU. <p>Primary Endpoint</p> <ul style="list-style-type: none">• Overall Response Rate (ORR) at Week 26 of rituximab-Pfizer and rituximab-EU based on central review in accordance with the revised response criteria for malignant lymphoma.¹¹ <p>Secondary Endpoints</p> <ul style="list-style-type: none">• Safety characterized by type, incidence, severity, timing, seriousness, and relationship to study therapy of adverse events and laboratory abnormalities.• Time to Treatment Failure (TTF).• Progression-Free Survival (PFS).• Complete Remission (CR) rate at Week 26.• Duration of response.• Overall survival.• Peak and trough drug concentrations.• CD19-positive B-cell counts.• Incidence of anti-drug antibodies (ADA), including neutralizing antibodies (Nab), and safety associated with immune response.
<p>Study Design:</p>	<p>This is a double-blind, randomized, Phase 3 clinical trial evaluating the efficacy, safety, PK and immunogenicity of rituximab-Pfizer and rituximab-EU in patients with CD20-positive, low tumor burden, follicular lymphoma in the first-line treatment setting.</p> <p>To select patients appropriate for treatment with rituximab monotherapy in accordance with various international treatment guidelines, including the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO),^{4,5} the study will enroll patients with low tumor burden follicular lymphoma who are asymptomatic for lymphoma specific B-symptoms.</p> <p>Low tumor burden will be assessed according to the Groupe d'Etude</p>

	<p>des Lymphomes Folliculaires (GELF) criteria.⁶ Clinically non-significant elevations in serum lactate dehydrogenase (LDH) or β-2 microglobulin (≤ 1.5 times upper limit of normal) at Screening will be allowed. These patient eligibility criteria are similar to other recent randomized studies conducted with rituximab monotherapy in low tumor burden follicular lymphoma.⁷</p> <p>The hypothesis to be tested in this study is that the efficacy (ORR) of rituximab-Pfizer is similar to that of rituximab-EU. Retrospective histological confirmation of CD20-positive FL will be obtained by a central pathology review. Central imaging review will be performed for all disease assessments up through Week 52. The primary endpoint is Overall Response Rate (ORR) at Week 26 in accordance with the revised response criteria for malignant lymphoma.¹¹ Secondary endpoints include safety, TTF, PFS, CR, duration of response, OS, selected peak and trough drug concentrations, CD19-positive B-cell depletion, and immunogenicity.</p> <p>Approximately 394 patients will be randomized in a 1:1 ratio to receive rituximab-Pfizer or rituximab-EU. Randomization will be stratified by low, medium, and high risk patients using the Follicular Lymphoma International Prognostic Index 2 (FLIPI2).¹²</p> <p>Safety will be reviewed throughout the trial in a blinded manner by the study team and by an unblinded external Data Monitoring Committee (E-DMC).</p>
Study Treatments:	<p>During the study, patients will receive 4 weekly doses of rituximab-Pfizer or rituximab-EU administered via intravenous infusion. The dose of rituximab-Pfizer or rituximab-EU will be 375 mg/m^2 of body surface area.</p>
Statistical Methods:	<p>The primary hypothesis to be tested in this study is that the difference between the ORR of rituximab-Pfizer and that of rituximab-EU is within a pre-specified margin of -16% to 16%. A sample size of approximately 394 patients (197 per treatment arm) provides approximately 93% power for achieving equivalence under the specified margin with 2.5% type I error rate, assuming an ORR of 77% in both treatment arms.</p>

SCHEDULE OF ACTIVITIES

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to [Study Procedures](#) and [Assessments](#) sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the well being of the patient.

Study Period	Screening ¹	Treatment				Follow -Up		End of Study/ Early Termination
		Week 1 – 4				Week 5	Weeks 13, 26, 39	
Study Week	Day -56 to 0	Day 1	Day 8	Day 15	Day 22	Day 29	Approximately Every	Three Months
Visit Timing	Day -56 to 0	Day 1	Day 8	Day 15	Day 22	Day 29	Approximately Every	Three Months
Visit Number	1	2	3	4	5	6	7, 8, 9	10
Allowable Visit Window			±1 Day	±1 Day	±1 Day	±3 Days	±14 Days	
Informed Consent ²	X							
Inclusion/Exclusion Criteria ³	X	X						
Histological Confirmation of Diagnosis ⁴	X							
Demography	X							
Medical and Oncologic History	X							
Lymphoma-Related Signs & Symptoms	X	X	X	X	X	X	X	X
FLIPI& FLIPI2	X							
Prior Medications	X							
Complete Physical Examination ⁵	X							X
Targeted Physical Examination ⁶		X	X	X	X	X	X	
Vital Signs ⁷	X	X	X	X	X	X	X	X
ECOG Performance Status	X					X	X	X
Laboratory Testing ⁸								
Hematology	X	X				X	X	X
Chemistry	X	X				X	X	X
Urinalysis	X							X
Pregnancy Test ⁹	X	X						X
β2-microglobulin and LDH	X	X				X	X	X

Study Period	Screening ¹	Treatment				Follow -Up			End of Study/ Early Termination
Study Week		Week 1 – 4				Week 5	Weeks 13, 26, 39	Week 52	
Visit Timing	Day -56 to 0	Day 1	Day 8	Day 15	Day 22	Day 29	Approximately Every Three Months		
Visit Number	1	2	3	4	5	6	7, 8, 9	10	
Allowable Visit Window			±1 Day	±1 Day	±1 Day	±3 Days	±14 Days		
Viral Disease Screen ¹⁰	X								
Circulating lymphoma cells	X								
Electrocardiogram ¹¹	X							X	
[18F]FDG-PET/CT or CT Scan ¹²	X						X	X	
[18F]FDG-PET	X						X ¹³		
Bone Marrow Biopsy or Aspiration	X						X ¹⁴		
Randomization		X							
Serum PK Sampling ¹⁵		X	X	X	X	X	X	X	
CD19 ⁺ B-cell Count Sampling ¹⁶		X	X	X	X	X	X	X	
Immunogenicity Sampling ¹⁷		X		X		X	X	X	
IgG Sampling		X	X	X	X	X	X	X	
IgM Sampling		X	X	X	X	X	X	X	
Premedications ¹⁸		X	X	X	X				
Study Drug Administration		X	X	X	X				
Concomitant Medications		X	X	X	X	X	X	X	
Adverse Event Assessment		X	X	X	X	X	X	X	
Contraception Check ¹⁹		X	X	X	X	X	X	X	

1. The screening period may last up to 56 days (8 weeks). Patients must have all screening lab tests conducted within 28 days (4 weeks) of the first dose of study medication (Day 1).
2. Informed Consent must be obtained prior to the patient undergoing any study specific procedure and may occur prior to the screening period.
3. All eligibility requirements must be met in order to randomize a patient. Patients who do not meet all requirements at initial screening can be re-screened if appropriate.
4. Patients can be entered based on a diagnosis of CD20+ follicular lymphoma confirmed at the investigational site. Archival tissue or slides must be sent to the central pathology reviewer for confirmation of diagnosis. Patients must have tissue available for the central pathology review to be enrolled.
5. A complete physical examination is to be conducted at Screening (Visit 1) and End of Study/Early Termination (Visit 10 – Week 52). The genitourinary system may be excluded unless there are signs or symptoms involving that system. The PE must include a thorough assessment of the lymph nodes, liver and spleen.

6. Complete or targeted physical examinations must be conducted at study visits other than Screening and End of Study/Early Termination. Targeted PEs should be targeted to specific symptoms or complaints and be consistent with local standard of care. All Targeted PEs must include, at a minimum, an assessment of the lymph nodes, liver and spleen.
7. Vital signs include heart rate, seated blood pressure, respiratory rate, and oral or tympanic body temperature. On treatment days, vital signs should be monitored at least every 30 minutes (± 5 minutes) during rituximab administration and more frequently as necessary.
8. Screening laboratory tests must be conducted within 28 days of Day 1.
9. For female patients of childbearing potential, a serum pregnancy test will be performed during Screening and a urine pregnancy test will be performed on Day 1 prior to dosing. A serum pregnancy test will also be repeated at End of Study/Early Termination. Additional pregnancy tests should be performed whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests may also be conducted as requested by IRB/IECs or if required by local regulations.
10. Viral disease screening for hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), and hepatitis C antibody (HCVAb). HIV testing will be performed unless prohibited by local regulations.
11. 12-Lead electrocardiograms are required at Screening and at End of Study/Early Termination. ECGs should be performed after the patient has rested quietly for at least 10 minutes.
12. Diagnostic quality [18F]FDG-PET/CT or CT scan with contrast. Scans acquired up to 8 weeks prior to Day 1 may be used for Screening provided they are of adequate quality for central imaging review. The quality of the scan must be sufficient for accurate anatomical measurement of lymphoma lesions and for central review. PET/CT scans should be performed from the base of the skull to the proximal femurs; CT scans should include the neck, chest, abdomen, and pelvis. Patients for whom IV contrast is medically contraindicated should have an MRI of the neck, abdomen and pelvis and a non-contrast CT of the chest.
13. If the patient has not undergone an [18F]FDG-PET/CT, an [18F]FDG-PET scan from the base of the skull to the proximal femurs must be obtained at Screening. PET scans acquired up to 8 weeks prior to Day 1 may be used for Screening provided they are of adequate quality for central imaging review. For patients with positive findings at Screening who have not undergone PET/CT scans at the follow up visits, a second PET scan should be obtained during Follow-Up (Weeks 13-39) or at End of Study/Early Termination (Week 52) when a patient experiences a complete remission based on the investigator's review of the CT scan results. The follow-up PET should be performed within 4 weeks of the contrast enhanced CT.
14. Bone marrow biopsy or aspiration should be completed at Screening unless the patient has had a previous bone marrow biopsy or aspiration that was positive for bone marrow involvement. Bone marrow biopsies or aspirations done up to 12 weeks prior to Day 1 may be used for Screening. A second bone marrow biopsy is required during Follow-Up (Weeks 13-39) or at End of Study/Early Termination (Week 52) for patients who had bone marrow involvement at Screening and experience complete remission based on the investigator's review of the CT scan results. The follow-up bone marrow biopsy or aspiration should be performed within 4 weeks of the contrast enhanced PET/CT or CT.
15. On days where study drug is administered (Days 1, 8, 15, and 22), serum samples for measurement of drug concentrations will be collected prior to dose administration (within 4 hours of the start of dosing). On Days 1 and 22, additional drug concentration samples will also be collected within 15 minutes prior to the end of infusion. Additionally, drug concentration samples will also be collected at Weeks 5 (Day 29), 13, 26, 39 and 52.
16. Blood samples for analysis of CD19+ B-cell counts will be collected prior to dose administration on Days 1, 8, 15, and 22. Additional samples for analysis of CD19+ B-cell counts will be collected at Weeks 5 (Day 29), 13, 26, 39 and 52.

17. Serum samples for detection of anti-drug antibodies (ADA) and neutralizing antibodies (Nab) will be collected within 4 hours prior to dose administration on Day 1 and Day 15. Additional samples for detection of ADA and Nab will be collected at Weeks 5 (Day 29), 13, 26, 39, and 52.
18. Premedication with 100 mg IV methylprednisolone or its equivalent prior to the start of the study drug infusion. In addition, an anti-pyretic and an antihistamine (eg, paracetamol [acetaminophen] and diphenhydramine) should be administered before study drug infusion. Any reduction in dose of premedications after the first infusion should be in compliance with local labeling and regulations.
19. The investigator or a qualified-designee must confirm and document that all patients or their partners who are biologically capable of having children and are sexually active are using a highly effective method of contraception listed in [Section 4.4](#) consistently and correctly.

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1. INTRODUCTION

PF-05280586 (hereafter designated rituximab-Pfizer) is being developed as a potential biosimilar to rituximab. Rituximab is approved for two broad indications: musculoskeletal and connective tissue diseases and B-cell malignancies. Rituximab is an effective therapy for the treatment of patients with CD-20 positive, B-cell malignancies.^{1,2} Rituxan[®] is the commercially available product in the United States and will be referred to as rituximab-US; MabThera[®] is the commercially available product in the European Union and will be referred to as rituximab-EU. In Japan the commercially available product is Rituxan[®].

Rituximab is a chimeric monoclonal antibody comprised of a human IgG1_K Fc region and a murine variable region that binds specifically to human CD20. Rituximab contains 2 heavy (H) chains, each comprising 451 amino acids and 2 kappa light (L) chains each comprising of 213 amino acids, which are disulfide-bonded to form a 4-chain molecule (H₂L₂).

Rituximab-Pfizer has the same primary amino acid sequence as the commercially available rituximab product.

The term “biosimilar” refers to a biologic drug that is developed to be highly similar to an existing licensed reference biologic. Biosimilars are intended to treat the same diseases as the reference biologic using the same dose and treatment regimen. Unlike generic versions of chemically-synthesized small molecule therapies, biosimilars are not structurally identical to their reference biologic. This is due to the purity, characteristics, and activity of a specific biologic being dependent on, and sensitive to changes in the process by which it was manufactured. Therefore, the aim is to create a product with no clinically meaningful differences between the biosimilar and the reference biologic in terms of chemistry, manufacturing, and controls (CMC), purity, potency, pharmacokinetics (PK), safety, immunogenicity, and efficacy.

The demonstration of similarity in efficacy between a biosimilar and the innovator product is an essential component of a clinical trial program that collectively provides the evidence of biosimilarity. The current study will evaluate the efficacy, safety, PK, and immunogenicity of rituximab-Pfizer in patients with low tumor burden (LTB), CD20-positive, follicular lymphoma (FL) in the first-line treatment setting.

Throughout this clinical trial protocol, PF-05280586 is referred to as rituximab-Pfizer, however, biosimilarity has not yet been established and is not claimed. Likewise, the general term rituximab is sometimes used for convenience when discussing the 2 blinded study treatments but is not a claim of biosimilarity. Biosimilarity will be supported by analytical, non-clinical, clinical PK, pharmacodynamic (PD), safety and efficacy studies.

1.1. Indication

CD-20 positive, B-cell non-Hodgkin’s Lymphoma (NHL) is a heterogeneous group of malignancies with varying clinical outcomes.³ Classification of NHL is extremely complex and has undergone extensive revisions to include morphological, immunophenotypical, genetic, and clinical characteristics. This diverse set of diseases is characterized by varied pathogenesis and clinical outcomes that make management of NHL clinically challenging.

The risk of mortality from NHL depends on whether it is indolent or aggressive; indolent forms of NHL, such as follicular lymphoma (FL), have significantly better prognosis than more aggressive forms like diffuse large B cell lymphoma (DLBCL) and mantle cell lymphoma (MCL).

The current standard of care in advanced follicular lymphoma is rituximab in combination with chemotherapy. The indication for this study, anatomically defined, low tumor burden, CD-20 positive, follicular lymphoma, is a slow growing malignancy and rituximab monotherapy is an acceptable treatment option according to various treatment guidelines.^{5,6} The goal of treatment with rituximab monotherapy in LTB-FL is to relieve disease symptoms, to delay the time to more difficult to tolerate treatments such as chemotherapy, and to relieve the patient's anxiety related to disease.

To select patients appropriate for treatment with rituximab monotherapy in accordance with various international treatment guidelines, including NCCN and ESMO,^{5,6} the study will enroll patients with low tumor burden follicular lymphoma who are asymptomatic for lymphoma specific B-symptoms.

Low tumor burden will be assessed according to the Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria.⁶ Clinically non-significant elevations in serum LDH or β -2 microglobulin (≤ 1.5 times upper limit of normal) at Screening will be allowed. These patient eligibility criteria are similar to other recent randomized studies conducted with rituximab monotherapy in low tumor burden follicular lymphoma.^{7,8}

The current study will evaluate the efficacy, safety, pharmacokinetics, and immunogenicity of rituximab-Pfizer versus rituximab-EU in patients with CD20-positive, low tumor burden follicular lymphoma (LTB-FL) in the first-line treatment setting. Using rituximab monotherapy allows the assessment of biosimilarity without the potentially confounding factors that would be introduced by combining rituximab with chemotherapy in more advanced stage patients; this is particularly important for the assessment of comparative immunogenicity.

Pfizer has conferred with regulatory agencies in the US, EU, and Japan and has determined that treatment of patients with LTB-FL in the first line setting is acceptable in the context of a comparative trial of biosimilarity.

1.2. Background and Rationale

1.2.1. Rituximab

Rituximab is a chimeric monoclonal antibody comprised of a human IgG1_K Fc region and a murine variable region that binds specifically to human CD20. Rituximab is approved for the treatment of CD20-positive B-cell malignancies. It is estimated that over 500,000 patients with B cell lymphoma or leukemia have been treated with rituximab since market availability. Further information is contained within both the Investigators' Brochure (IB), and public information including the Summary of Product Characteristics for MabThera.

According to the rituximab prescribing information, the mechanism of action across the oncology indications is believed to be that rituximab binds specifically to the antigen CD20 (human B-lymphocyte-restricted differentiation antigen, Bp35). The antigen, a hydrophobic transmembrane protein located on pre-B and mature B lymphocytes, is expressed on 90% of B-cell NHL. CD20 is not found on hematopoietic stem cells, pro-B-cells, normal plasma cells, or other normal tissues. CD20 regulates an early step(s) in the activation process for cell cycle initiation and differentiation, and possibly functions as a calcium ion channel. Free CD20 is not found in circulating blood.

The Fab domain of rituximab binds to the CD20 antigen on B lymphocytes, and the Fc domain recruits immune effector functions to mediate B-cell lysis in vitro. Possible mechanisms of cell lysis include complement-dependent cytotoxicity (CDC) and antibody-dependent cell mediated cytotoxicity (ADCC). Rituximab binding was observed on lymphoid cells in the thymus, the white pulp of the spleen, and a majority of B lymphocytes in peripheral blood and lymph nodes. Little or no binding was observed in the non-lymphoid tissues examined.

Multiple clinical trials were conducted that allowed approval of multiple indications within CD20-positive B-cell malignancies for rituximab. Indications for the use of rituximab as a single agent in FL that appear to be uniform across multiple regions including the US, EU, and Japan include:

- Relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL;
- Maintenance therapy in patients achieving a complete or partial response to Rituxan in combination with chemotherapy;
- Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL after first-line CVP chemotherapy.

Many patients with follicular lymphoma present with advanced, but asymptomatic disease. Several randomized, controlled trials have shown there is no benefit in overall survival to treating these subjects with chemotherapy immediately. Therefore, many of these patients are followed (watchful waiting) rather than treated immediately. However, these older studies all evaluated toxic chemotherapeutic regimens. The use of single-agent rituximab has the potential to serve as a useful alternative to watchful waiting by delaying the time to initiation of chemotherapy. A recent study evaluated the use of 4 weekly doses of 375 mg/m² of rituximab and demonstrated a delay in the time to next treatment.⁷ The estimated median time to initiation of new therapy for watchful waiting in this study was 33 months, similar to a previous trial of watchful waiting.⁹ The time to initiation of new therapy was significantly longer in the rituximab monotherapy arm (p value of log-rank test <0.001) and the median time had not been reached at 4 years. While the use of rituximab monotherapy as a first-line treatment of LTB-FL is not indicated in the US or EU, it is an acceptable treatment option^{4,5} and has the potential to replace watchful waiting as the treatment of choice for asymptomatic, low tumor burden FL patients.

1.2.1.1. Efficacy of Rituximab Monotherapy in Low Tumor Burden Follicular Lymphoma

For patients with asymptomatic, advanced stage, follicular lymphoma, immediate chemotherapy when compared with a watch and wait approach shows no benefit. Deferring chemotherapy spares the patient of the side effects of the chemotherapy. Rituximab has a favorable side effect profile compared to chemotherapy, so a study was conducted to compare a watchful waiting approach versus immediate treatment with rituximab in patients with low tumor burden follicular lymphoma (LTB-FL).⁷

Adult patients with asymptomatic Stage II, III or IV follicular lymphoma (Grades 1–2 & 3a) were randomly assigned in a ratio of 1:1:1 to watchful waiting (Arm A), rituximab 375 mg/m² weekly for 4 weeks (Arm B) or rituximab 375 mg/m² weekly for 4 weeks followed by rituximab maintenance every 2 months for 2 years (from Month 3 to Month 25) (Arm C). The primary endpoints were time to initiation of new therapy (chemotherapy or radiotherapy) and effect on quality of life. After an interim analysis, the rituximab without maintenance group (Arm B) was discontinued. Overall response rate was assessed by investigators using the 1999 Response Criteria for Lymphoma¹⁰ at Month 7, 13 and 25.

There were 463 patients who were randomized (187 Arm A, 84 Arm B, and 192 Arm C) with 95% of patients having low tumor burden by GELF criteria. The other 5% had raised LDH but fulfilled the remaining GELF criteria. Responses were assessed at Months 7, 13 and 25. At Month 7, Arm A had a spontaneous remission rate (CR)=2% and a PR=4%, (ORR=6%). Arm B had a CR+CRu=47% and a PR=30% (ORR=77%). Arm C had a CR+CRu=59% and a PR=29% (ORR=88%). The estimated median time to initiation of new therapy in Arm A was 33 months.

There was a significant difference observed in the time to start of new treatment, with 46% (95% CI 39–53) of patients in the watchful waiting group not needing treatment at 3 years compared with 88% (83–92) in the maintenance rituximab group (hazard ratio [HR] 0.21, 95% CI 0.14–0.31; p<0.0001). 78% (95% CI 69–87) of patients in the rituximab induction group did not need treatment at 3 years, which was significantly more than in the watchful waiting group (HR 0.35, 95% CI 0.22–0.56; p<0.0001), but no different compared with the maintenance rituximab group (0.75, 0.41–1.34; p=0.33). These data indicate that initial treatment with rituximab significantly delays the need for new therapy.

Another study, RESORT, looked at the role of maintenance therapy in patients with LTB-FL who received single agent rituximab.⁸ Patients received 4 doses of rituximab (375 mg/m²) and responders were randomized to maintenance rituximab (MR - single dose rituximab every 3 months) or rituximab retreatment (RR - rituximab weekly x 4 at disease progression). Each strategy was continued until treatment failure and the primary endpoint was time to treatment failure (TTF). There were 384 patients enrolled. Complete or partial response was achieved in 274 patients (71%), who were then randomized to MR (n=140) or RR (n=134). The mean number of rituximab doses/patient (including the 4 induction doses) was 15.8 (range 5- 31) for MR and 4.5 (range 4-16) for RR. With a median follow-up of 3.8 yrs, TTF was 3.9 years for MR versus 3.6 years for RR (p=NS). At 12 months post randomization, there was no discernible difference in health related quality of life and

anxiety between the two arms. This study suggested that there was no advantage of rituximab maintenance therapy over rituximab treatment at progression after rituximab induction treatment in LTB-FL.

1.2.1.2. Safety of Rituximab

The safety profile of rituximab is described in the Summary of Product Characteristics (SPC) for MabThera (rituximab).²

Rituximab is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients or to murine proteins.

According to the SPC the following (as abstracted) are special warnings and precautions for use in patients with non-Hodgkin's lymphoma:

Infusion related adverse reactions including cytokine release syndrome accompanied by hypotension and bronchospasm have been observed in 10 % of patients treated with MabThera. These symptoms are usually reversible with interruption of MabThera infusion and administration of an anti-pyretic, an antihistaminic, and, occasionally, oxygen, intravenous saline or bronchodilators, and glucocorticoids if required.

Anaphylactic and other hypersensitivity reactions have been reported following the intravenous administration of proteins to patients. In contrast to cytokine release syndrome, true hypersensitivity reactions typically occur within minutes after starting infusion. Medicinal products for the treatment of hypersensitivity reactions, eg, epinephrine (adrenaline), antihistamines and glucocorticoids, should be available for immediate use in the event of an allergic reaction during administration of MabThera.

Clinical manifestations of anaphylaxis may appear similar to clinical manifestations of the cytokine release syndrome. Reactions attributed to hypersensitivity have been reported less frequently than those attributed to cytokine release.

Since hypotension may occur during MabThera infusion, consideration should be given to withholding anti-hypertensive medicines 12 hours prior to the MabThera infusion.

Angina pectoris, or cardiac arrhythmias such as atrial flutter and fibrillation heart failure or myocardial infarction have occurred in patients treated with MabThera. Therefore patients with a history of cardiac disease and/or cardiotoxic chemotherapy should be monitored closely.

Very rare cases of hepatitis B reactivation have been reported in subjects receiving rituximab including fulminant hepatitis with fatal outcome. The majority of these subjects were also exposed to cytotoxic chemotherapy. The reports are confounded by both the underlying disease state and the cytotoxic chemotherapy. Patients with a history of hepatitis B infection should be carefully monitored for signs of active hepatitis B infection.

Very rare cases of Progressive Multifocal Leukoencephalopathy (PML) have been reported during post-marketing use of MabThera in NHL. The majority of patients had received rituximab in combination with chemotherapy or as part of a hematopoietic stem cell

transplant. Physicians treating patients with non-Hodgkin's lymphoma should consider PML in the differential diagnosis of patients reporting neurological symptoms and consultation with a Neurologist should be considered as clinically indicated.

The safety of immunization with any vaccine, particularly live viral vaccines, following MabThera therapy has not been studied. The ability to generate a primary or anamnestic humoral response to any vaccine has also not been studied.

Pregnancy

IgG immunoglobulins are known to cross the placental barrier. B cell levels in human neonates following maternal exposure to MabThera have not been studied in clinical trials. There are no adequate and well-controlled data from studies in pregnant women, however transient B-cell depletion and lymphocytopenia have been reported in some infants born to mothers exposed to rituximab during pregnancy. For these reasons MabThera/Rituxan should not be administered to pregnant women unless the possible benefit outweighs the potential risk.

Due to the long retention time of rituximab in B cell depleted patients, women of childbearing potential should use effective contraceptive methods during treatment and for 12 months following MabThera therapy.

Developmental toxicity studies performed in cynomolgus monkeys revealed no evidence of embryotoxicity in utero. New born offspring of maternal animals exposed to MabThera were noted to have depleted B cell populations during the post natal phase.

Lactation

Whether rituximab is excreted in human milk is not known. However, because maternal IgG is excreted in human milk, and rituximab was detectable in milk from lactating monkeys, women should not breastfeed while treated with MabThera and for 12 months following MabThera treatment.

Effects on ability to drive and use machines

No studies on the effects of MabThera on the ability to drive and use machines have been performed, although the pharmacological activity and adverse events reported to date do not indicate that such an effect is likely.

Overall safety profile of MabThera in non-Hodgkin's lymphoma

The overall safety profile of MabThera in non-Hodgkin's lymphoma is based on data from patients from clinical trials and from post-marketing surveillance. These patients were predominantly treated either with MabThera monotherapy (as induction treatment or maintenance treatment following induction treatment) or in combination with chemotherapy.

The most frequently observed adverse drug reactions (ADRs) in patients receiving MabThera were infusion-related reactions which occurred in the majority of patients during the first infusion. The incidence of infusion-related symptoms decreases substantially with subsequent infusions and is less than 1% after eight doses of MabThera.

Infectious events (predominantly bacterial and viral) occurred in approximately 30-55 % of patients during clinical trials in patients with NHL.

The most frequent reported or observed serious adverse drug reactions were infusion-related reactions (including cytokine-release syndrome, tumour-lysis syndrome), infections, and cardiovascular events. Other serious ADRs reported include hepatitis B reactivation and PML.

The frequencies of ADRs reported with MabThera alone or in combination with chemotherapy are summarized in the SPC.

Infusion-related reactions

Signs and symptoms suggestive of an infusion-related reaction were reported in more than 50% of patients in clinical trials, and were predominantly seen during the first infusion, usually in the first one to two hours. These symptoms mainly comprised fever, chills and rigors. Other symptoms included flushing, angioedema, bronchospasm, vomiting, nausea, urticaria/rash, fatigue, headache, throat irritation, rhinitis, pruritus, pain, tachycardia, hypertension, hypotension, dyspnoea, dyspepsia, asthenia and features of tumor lysis syndrome. Severe infusion-related reactions (such as bronchospasm, hypotension) occurred in about 10 % of the cases. Additional reactions reported in some cases were myocardial infarction, atrial fibrillation and pulmonary oedema. Exacerbations of pre-existing cardiac conditions such as angina pectoris or congestive heart failure or severe cardiac events (heart failure, myocardial infarction, atrial fibrillation), pulmonary oedema, multi-organ failure, tumour lysis syndrome, cytokine release syndrome, renal failure, and respiratory failure were reported at lower or unknown frequencies. The incidence of infusion-related symptoms decreased substantially with subsequent infusions and is <1 % of patients by the eighth cycle of MabThera-containing treatment.

Infections

MabThera induces B-cell depletion in about 70-80% of patients, but was associated with decreased serum immunoglobulins only in a minority of patients.

Localized candida infections as well as Herpes zoster was reported at a higher incidence in the MabThera-containing arm of randomized studies. Severe infections were reported in about 4% of patients. Higher frequencies of infections overall, including grade 3 or 4 infections, were observed during MabThera maintenance treatment up to 2 years when compared to observation. There was no cumulative toxicity in terms of infections reported over a 2-year treatment period. In addition, other serious viral infections either new, reactivated or exacerbated, some of which were fatal, have been reported with MabThera treatment. The majority of patients had received MabThera in combination with

chemotherapy or as part of a hematopoietic stem cell transplant. Examples of these serious viral infections are infections caused by the herpes viruses (Cytomegalovirus, Varicella Zoster Virus and Herpes Simplex Virus), JC virus (progressive multifocal leukoencephalopathy (PML)) and hepatitis C virus. Cases of hepatitis B reactivation, have been reported, the majority of which were in subjects receiving MabThera in combination with cytotoxic chemotherapy. Progression of Kaposi's sarcoma has been observed in rituximab-exposed patients with pre-existing Kaposi's sarcoma. These cases occurred in non-approved indications and the majority of patients were HIV positive.

Haematologic Adverse Reactions

In clinical trials with MabThera monotherapy given for 4 weeks, haematological abnormalities occurred in a minority of patients and were usually mild and reversible. Severe (grade 3/4) neutropenia was reported in 4.2 %, anaemia in 1.1 % and thrombocytopenia in 1.7 % of the patients. During MabThera maintenance treatment for up to 2 years, leucopenia (5% vs 2%, grade 3/4) and neutropenia (10% vs.4%, grade 3/4) were reported at a higher incidence when compared to observation. The incidence of thrombocytopenia was low (<1, grade 3/4%) and was not different between treatment arms. In studies with MabThera in combination with chemotherapy, grade 3/4 leucopenia (88% vs 79%), neutropenia (R-CVP 24% vs CVP 14%; R-CHOP 97% vs. CHOP 88%) were reported higher frequencies when compared to chemotherapy alone. However, the higher incidence of neutropenia in patients treated with MabThera and chemotherapy was not associated with a higher incidence of infections and infestations compared to patients treated with chemotherapy alone and the neutropenia was not prolonged in the MabThera group. There were no differences reported for the incidence of thrombocytopenia or anaemia. Some cases of late neutropenia occurring more than four weeks after the last infusion of MabThera were reported.

Cardiovascular reactions

Cardiovascular reactions during clinical trials with MabThera monotherapy were reported in 18.8 % of patients with the most frequently reported events being hypotension and hypertension. Cases of grade 3 or 4 arrhythmia (including ventricular and supraventricular tachycardia) and angina pectoris during infusion were reported. During maintenance treatment, the incidence of grade 3/4 cardiac disorders was comparable between patients treated with MabThera and observation. Cardiac events were reported as serious adverse events (including atrial fibrillation, myocardial infarction, left ventricular failure, myocardial ischemia) in 3 % of patients treated with MabThera compared to <1% on observation. In studies evaluating MabThera in combination with chemotherapy, the incidence of grade 3 and 4 cardiac arrhythmias, predominantly supraventricular arrhythmias such as tachycardia and atrial flutter/fibrillation, was higher in the R-CHOP group (14 patients, 6.9 %) as compared to the CHOP group (3 patients, 1.5 %). All of these arrhythmias either occurred in the context of a MabThera infusion or were associated with predisposing conditions such as fever, infection, acute myocardial infarction or pre-existing respiratory and cardiovascular disease.

Neurologic events

During the treatment period, four patients (2 %) treated with R-CHOP, all with cardiovascular risk factors, experienced thromboembolic cerebrovascular accidents during the first treatment cycle. There was no difference between the treatment groups in the incidence of other thromboembolic events. In contrast, three patients (1.5 %) had cerebrovascular events in the CHOP group, all of which occurred during the follow-up period.

Gastrointestinal Disorders

Gastrointestinal perforation in some cases leading to death has been observed in patients receiving MabThera for treatment of non Hodgkin's lymphoma. In the majority of these cases, MabThera was administered with chemotherapy.

IgG levels

In the clinical trial evaluating MabThera maintenance treatment, median IgG levels were below the lower limit of normal (LLN) (<7 g/L) after induction treatment in both the observation and the MabThera groups. In the observation group, the median IgG level subsequently increased to above the LLN, but remained constant in the MabThera group. The proportion of patients with IgG levels below the LLN was about 60% in the MabThera group throughout the 2 year treatment period, while it decreased in the observation group (36 % after 2 years).

Elderly patients (≥65 years):

The incidence of ADRs of all grades and grade 3 /4 ADR was similar in elderly patients compared to younger patients (<65 years).

1.2.1.3. Immunogenicity

Immunogenicity of rituximab is discussed in the US Prescribing information for Rituxan[®] (rituximab).

As with all therapeutic proteins, there is a potential for immunogenicity. The observed incidence of antibody (including neutralizing antibody) positivity in an assay is highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Rituxan with the incidence of antibodies to other products may be misleading.

Using an ELISA assay, anti-human anti-chimeric antibody (HACA) was detected in 4 of 356 (1.1%) patients with low-grade or follicular NHL receiving single-agent Rituxan. Three of the four patients had an objective clinical response.

1.2.1.4. Pharmacokinetics

The pharmacokinetics of rituximab are described in the MabThera SPC.

Based on a population pharmacokinetic analysis in 298 NHL patients who received single or multiple infusions of rituximab as a single agent or in combination with CHOP therapy (applied rituximab doses ranged from 100 to 500 mg/m²), the typical population estimates of nonspecific clearance (CL1), specific clearance (CL2) likely contributed by B cells or tumor burden, and central compartment volume of distribution (V1) were 0.14 L/day, 0.59 L/day, and 2.7 L, respectively. The estimated median terminal elimination half-life of rituximab was 22 days (range, 6.1 to 52 days). Baseline CD19-positive cell counts and size of measurable tumor lesions contributed to some of the variability in CL2 of rituximab in data from 161 patients given 375 mg/m² as an intravenous infusion for 4 weekly doses. Patients with higher CD19-positive cell counts or tumor lesions had a higher CL2. However, a large component of inter-individual variability remained for CL2 after correction for CD19-positive cell counts and tumor lesion size. V1 varied by body surface area (BSA) and CHOP therapy. This variability in V1 (27.1% and 19.0%) contributed by the range in BSA (1.53 to 2.32 m²) and concurrent CHOP therapy, respectively, were relatively small. Age, gender and WHO performance status had no effect on the pharmacokinetics of rituximab. This analysis suggests that dose adjustment of rituximab with any of the tested covariates is not expected to result in a meaningful reduction in its pharmacokinetic variability.

Rituximab, administered as an intravenous infusion at a dose of 375 mg/m² at weekly intervals for 4 doses to 203 patients with NHL naive to rituximab, yielded a mean C_{max} following the fourth infusion of 486 µg/mL (range, 77.5 to 996.6 µg/mL). Rituximab was detectable in the serum of patients 3 – 6 months after completion of last treatment. Upon administration of rituximab at a dose of 375 mg/m² as an intravenous infusion at weekly intervals for 8 doses to 37 patients with NHL, the mean C_{max} increased with each successive infusion, spanning from a mean of 243 µg/mL (range, 16 – 582 µg/mL) after the first infusion to 550 µg/mL (range, 171 – 1177 µg/mL) after the eighth infusion.

1.2.1.5. Pharmacodynamics

The following is a reprint of the information pertaining to rituximab-EU pharmacodynamics in patients with NHL in the MabThera SPC:

Rituximab binds specifically to the transmembrane antigen, CD20, a non-glycosylated phosphoprotein, located on pre-B and mature B lymphocytes. The antigen is expressed on >95% of all B cell non-Hodgkin's lymphomas.

CD20 is found on both normal and malignant B cells, but not on haematopoietic stem cells, pro-B cells, normal plasma cells or other normal tissue. This antigen does not internalise upon antibody binding and is not shed from the cell surface. CD20 does not circulate in the plasma as a free antigen and, thus, does not compete for antibody binding.

The Fab domain of rituximab binds to the CD20 antigen on B lymphocytes and the Fc domain can recruit immune effector functions to mediate B cell lysis. Possible mechanisms of effector-mediated cell lysis include complement-dependent cytotoxicity (CDC) resulting

from C1q binding, and antibody-dependent cellular cytotoxicity (ADCC) mediated by one or more of the Fcγ receptors on the surface of granulocytes, macrophages and NK cells. Rituximab binding to CD 20 antigen on B lymphocytes has also been demonstrated to induce cell death via apoptosis.

Peripheral B cell counts declined below normal following completion of the first dose of MabThera. In patients treated for hematological malignancies, B cell recovery began within 6 months of treatment and generally returned to normal levels within 12 months after completion of therapy, although in some patients this may take longer (up to a median recovery time of 23 months post-induction therapy).

1.2.2. Rituximab-Pfizer (PF-05280586)

Rituximab-Pfizer (PF-05280586) is an investigational, genetically engineered chimeric mouse/human IgG1 monoclonal antibody (mAb) directed against the CD20 antigen. Rituximab-Pfizer contains 2 heavy (H) chains, each comprising 451 amino acids and 2 kappa light (L) chains each comprising of 213 amino acids, which are disulfide-bonded to form a 4-chain molecule (H₂L₂). Rituximab-Pfizer has the same primary amino acid sequence as rituximab-EU (MabThera) and rituximab-US (Rituxan) and is being developed to be similar to the licensed products. Reference the PF-05280586 Investigator's Brochure (IB) for further details.

CCI



1.2.3. Drug Product Similarity

The development of rituximab-Pfizer has focused on molecular and functional similarity to rituximab-EU. The physicochemical and functional characterization has demonstrated a high degree of similarity between these products as described in the Investigator's Brochure. Reference the IB for further definition of parameters and most recent information on product characterization.

1.2.4. Rationale

The evaluation of efficacy and safety (including immunogenicity assessment) between a biosimilar and the innovator product is an essential component of an efficient clinical trial program collectively providing the evidence of biosimilarity. The current study will compare

the efficacy, safety, pharmacokinetics, and immunogenicity of rituximab-Pfizer in patients with low tumor burden (LTB), CD20-positive, follicular lymphoma (FL) in the first-line treatment setting. While the use of rituximab monotherapy as first-line treatment of LTB-FL is not indicated in the US or EU, it is a standard of care (SOC)^{4,5} and has the potential to replace watchful waiting as the treatment of choice for asymptomatic, low tumor burden FL patients.

1.3. Single Reference Safety Document

Complete information for this compound may be found in the Single Reference Safety Document (SRSD), which for this study is the Investigator's Brochure. The Single Reference Safety Document for the comparator agent is the Summary of Product Characteristics (SPC) for MabThera.²

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objective

- To compare the efficacy of rituximab-Pfizer to rituximab-EU when administered as a first-line treatment to patients with CD20-positive, low tumor burden follicular lymphoma (LTB-FL).

2.1.2. Secondary Objectives

- To evaluate the safety of rituximab-Pfizer and rituximab-EU.
- To evaluate the population pharmacokinetics of rituximab-Pfizer and rituximab-EU.
- To evaluate the immunogenicity of rituximab-Pfizer and rituximab-EU.
- To characterize CD19-positive B-cell depletion and recovery in patients receiving rituximab-Pfizer and rituximab-EU.

2.2. Endpoints

2.2.1. Primary Endpoint

- Overall Response Rate (ORR) at Week 26 of rituximab-Pfizer and rituximab-EU based on central review in accordance with the revised response criteria for malignant lymphoma.¹¹

2.2.2. Secondary Endpoints

- Safety characterized by type, incidence, severity, timing, seriousness, and relationship to study therapy of adverse events and laboratory abnormalities.
- Time to Treatment Failure (TTF).

- Progression-Free Survival (PFS).
- Complete Remission (CR) rate at Week 26.
- Duration of response.
- Overall survival.
- Peak and trough drug concentrations.
- CD19-positive B-cell counts.
- Incidence of anti-drug antibodies (ADA), including neutralizing antibodies (NAb), and safety associated with immune response.

3. STUDY DESIGN

This is a double-blind, randomized, Phase 3 clinical trial evaluating the efficacy, safety, PK and immunogenicity of rituximab-Pfizer versus rituximab-EU in patients with CD20-positive, low tumor burden, follicular lymphoma in the first-line treatment setting.

The study will enroll patients with low tumor burden follicular lymphoma who are asymptomatic for lymphoma specific B-symptoms. Low tumor burden will be assessed according to the Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria.⁶ Clinically non-significant elevations in serum LDH or β -2 microglobulin (≤ 1.5 times upper limit of normal) at Screening will be allowed. These patient eligibility criteria are similar to other recent randomized studies conducted with rituximab monotherapy in low tumor burden follicular lymphoma.^{7,8}

Retrospective histological confirmation of CD20-positive FL will be obtained by a central pathology review. Central imaging review will be performed for all disease assessments up through Week 52. The primary endpoint is Overall Response Rate (ORR) at Week 26 in accordance with the revised response criteria for malignant lymphoma.¹¹ Secondary endpoints include safety, TTF, PFS, CR, duration of response, OS, selected peak and trough drug concentrations, CD19-positive B-cell depletion, and immunogenicity.

Approximately 394 Patients will be randomized in a 1:1 ratio to receive rituximab-Pfizer or rituximab-EU. Randomization will be stratified by low, medium, and high risk patients using the Follicular Lymphoma International Prognostic Index 2 (FLIPI2).¹² During the study, patients will receive 4 weekly doses of rituximab-Pfizer or rituximab-EU administered via intravenous infusion. The dose of rituximab-Pfizer or rituximab-EU will be 375 mg/m² of body surface area. The maximum dose that can be administered is 1125 mg.

Safety will be reviewed throughout the trial in a blinded manner by the study team and in an unblinded manner by an external Data Monitoring Committee (E-DMC). Population PK assessment for rituximab-Pfizer and rituximab-EU will be conducted in this study. Serum samples for determination of drug concentrations will be collected at specified time points.

The primary hypothesis to be tested in this study is that the efficacy of rituximab-Pfizer as measured by the ORR is similar to rituximab-EU. Using ORR as determined by the one randomized trial of watchful waiting versus rituximab administered as a first-line treatment to patients with low tumor burden CD20+ FL⁷ a trial of at least 394 patients will be required to demonstrate similarity.

4. PATIENT SELECTION

This study can fulfill its objectives only if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular patient.

4.1. Inclusion Criteria

Patient eligibility should be reviewed and documented by an appropriately qualified member of the investigator's study team before patients are included in the study.

Patients must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Male or female patients aged 18 years (or local age of maturity for providing informed consent if greater than 18 years) or older.
2. Histologically confirmed, Grade 1-3a, CD20-positive follicular lymphoma (containing no elements of diffuse large B-cell lymphoma).

NOTE: Patients can be entered based on a diagnosis of CD20+ follicular lymphoma confirmed at the investigational site. Archival tissue or slides must be sent to the central pathology reviewer for confirmation of diagnosis. Patients must have tissue specimens available for the central pathology review to be enrolled.

3. Ann Arbor Stage II, III, or IV ([Appendix 1](#)).
4. Eastern Cooperative Oncology Group (ECOG) status of 0 to 1.
5. At least 1 measureable disease lesion identifiable by imaging:
 - A nodal lesion must be at least 11 mm x 11 mm OR ≥ 16 mm in the greatest transverse diameter [regardless of short axis measurement].
 - An extranodal lesion must be at least 10 mm x 10 mm.
6. Patient has low tumor burden FL, defined as:
 - a. Serum LDH ≤ 1.5 upper limit of normal.
 - b. $\beta 2$ -microglobulin ≤ 1.5 upper limit of normal.

- c. Largest nodal or extra-nodal mass <7 cm in diameter.
- d. No more than 3 nodal sites with a diameter >3 cm.
- e. No clinically significant serous effusions detectible on chest radiography.
- f. Spleen enlargement ≤16 cm by CT (computed tomography) scan.
- g. No complications such as organ compression or impairment.
- h. No B symptoms:
 - fever >38°C for 3 consecutive days;
 - recurrent, drenching night sweats;
 - unintentional weight loss exceeding 10% body weight in 6 months.

NOTE: Patients with mild FL symptoms may be enrolled in the study as long as they do not meet the criteria for B symptoms.

7. Men and women of childbearing potential must agree to use a highly effective method of contraception throughout the study and for 12 months after the last dose of assigned treatment. A man or woman is of childbearing potential if, in the opinion of the investigator, he or she is biologically capable of having children and is sexually active.
8. Evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study.
9. Patients who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

4.2. Exclusion Criteria

Patients presenting with any of the following will not be included in the study:

1. Patients who are not candidates for rituximab monotherapy in the opinion of the investigator.
2. Evidence of histologic transformation to high-grade or diffuse large B-cell lymphoma.
3. Central nervous system or meningeal involvement or cord compression by the lymphoma (Brain imaging is not required, but may be conducted if clinically indicated).
4. Any previous history of T-cell lymphoma.

5. Patients with $\geq 5000/\text{mm}^3$ circulating lymphoma cells.
6. Any prior systemic therapy for B-cell NHL, including chemotherapy, immunotherapy, or steroids. Patients may have received prior localized radiotherapy for FL (Low dose [10 mg oral prednisone or equivalent] or inhaled steroids for other conditions are acceptable).
7. Any prior treatment with rituximab.
8. Hypersensitivity to the active substances or to any of the excipients in rituximab-Pfizer or rituximab-EU.
9. History of allergy or prior hypersensitivity to murine, chimeric, humanized, or human monoclonal antibody treatments.
10. Impaired bone marrow function as evidenced by hemoglobin < 9.0 g/dL, absolute neutrophil count (ANC) $< 1.5 \times 10^9$ cells/L ($1500/\text{mm}^3$) or a platelet count $< 75 \times 10^9$ cells/L ($75,000/\text{mm}^3$).
11. Symptomatic ischemic heart disease or NYHA Class II, III, or IV congestive heart failure.
12. Active infection with tuberculosis (TB). Patients with evidence of latent TB or a history of TB must have completed treatment or have initiated treatment for at least 1 month before the first dose of study treatment (Day 1). TB testing is required only if it is required by local regulations or practice.
13. Positive test for hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), or anti-hepatitis C antibody (HCVAb), or seropositivity for human immunodeficiency virus (HIV).
14. Any other active uncontrolled infection. Patients with an infection must have initiated a course of treatment with an effective antimicrobial a minimum of 7 days before the first dose of study treatment (Day 1) and be free of symptoms from the infection.
15. Any history of another cancer during the last 5 years with the exception of non-melanoma skin tumors, in situ cervical carcinoma, or in situ breast cancer treated with curative intent with no history of metastatic disease.
16. Administration of a live vaccine ≤ 6 weeks before first dose of study treatment (Day 1).
17. Major surgery ≤ 28 days before first dose of study treatment.

18. Anticipated need for concomitant administration of any other experimental drug, or a concomitant chemotherapy, anticancer hormonal therapy, radiotherapy, or immunotherapy during study participation.
19. Participation in other studies involving investigational drug(s) (Phases 1-4) within 4 weeks or 5 half-lives, whichever is longer, before the current study begins and/or during study participation.
20. Any other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.
21. Patients who are investigational site staff members directly involved in the conduct of the trial and their family members, site staff members otherwise supervised by the investigator, or patients who are Pfizer employees directly involved in the conduct of the trial.
22. Pregnant females; breastfeeding females; males and females of childbearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for 12 months after last dose of investigational product.
23. Patients with a body surface area $>3.0 \text{ m}^2$.

4.3. Randomization Criteria

Patients who have signed informed consent to participate in the study, have undergone all screening procedures, and meet all inclusion and exclusion criteria for participation in the trial, may be randomized into this study. Randomization will be conducted using a web-based automated response system (IMPALA). Patients should be randomized on Day 1 if at all possible; however, patients may be randomized up to 5 business days in advance of Day 1 if required in order to allow time to dispense the study drug and ensure receipt at the site. Sponsor confirmation of eligibility must be obtained prior to randomization of patients.

4.4. Life Style Guidelines

All male patients who are able to father children and female patients who are of childbearing potential, and are sexually active and at risk for pregnancy must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for 12 months after the last dose of investigational product. The investigator, in consultation with the patient, will select the most appropriate method of contraception for the individual patient from the permitted list of contraception methods, and instruct the patient in its consistent and correct use. The investigator, at each study visit, will confirm and document consistent and correct use. In addition, the investigator will instruct the patient to call immediately if the selected birth control method is discontinued or if pregnancy is known or suspected.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include:

1. Established use of oral, inserted, injected or implanted hormonal methods of contraception are allowed provided the patient remains on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.
2. Correctly placed copper containing intrauterine device (IUD).
3. Male sterilization with appropriately confirmed absence of sperm in the post-vasectomy ejaculate.
4. Bilateral tubal ligation or bilateral salpingectomy.

4.5. Sponsor Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the trial is documented in the study contact list. To facilitate access to appropriately qualified medical personnel on study related medical questions or problems, patients are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, patient study number, contact information for the investigational site and contact details for a help desk in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the patients participation in the study. The help desk number can also be used by investigational staff if they are seeking advice on medical questions or problems, however it should only be used in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace the established communication pathways between the investigational site and study team for advice on medical questions or problems that may arise during the study. The help desk number is not intended for use by the patient directly and if a patient calls that number they will be directed back to the investigational site.

5. STUDY TREATMENTS

5.1. Allocation to Treatment

This study is a double-blind, randomized clinical trial.

After a patient has provided written informed consent and completed the necessary Screening assessments, the clinical site must complete an Eligibility Review Form and send to the sponsor for approval of randomization. Upon receipt of the sponsor's approval, the site may randomize the patient in IMPALA.

A computer-generated randomization schedule will be used to assign patients to the treatment groups. Patients will be assigned a patient number in the order of their acceptance into the study. This identifying number will be retained throughout the study.

Following signing of informed consent, patients will be registered into the study using an automated web-based randomization system (IMPALA) provided by the sponsor to receive a unique patient identification number. Randomization will be performed using IMPALA. Patients will be randomized in a 1:1 ratio to one of the 2 study treatment arms:

- Arm A: Rituximab-Pfizer
- Arm B: Rituximab-EU (MabThera)

Randomization will be stratified by low, medium, and high risk patients using the Follicular Lymphoma International Prognostic Index 2 (FLIPI2).

5.2. Breaking the Blind

This double-blind study will be blinded to the patients and investigator/site staff, with the exception of the pharmacy staff preparing study treatment infusions. The study will be conducted in a double blinded fashion through Week 26 when the primary endpoint will be evaluated. Prior to Week 26, the patients, investigators and sponsor will be blinded to randomized study treatments. After Week 26, some members of the study team will be unblinded so that a study report for the corresponding data collected through Week 26 can be generated. The patients and investigators will continue to be blinded to individual study treatments until the end of the study.

At the initiation of the study, the study site will be instructed on using IMPALA for breaking the blind. Blinding should only be broken in emergency situations for reasons of individual patient safety when knowledge of the investigational product (IP) assignment is required for medical management. At all other times, treatment and randomization information will be kept confidential and will not be released to the investigator/study staff until the conclusion of the study.

If the blind for a patient has been broken, the Sponsor must be notified and the reason must be fully documented in source documents and entered on the electronic Case Report Form (eCRF). Any adverse event (AE) or serious adverse event (SAE) associated with breaking the blind must be recorded and reported as specified in this protocol.

5.3. Drug Supplies

5.3.1. Formulation and Packaging

Rituximab-Pfizer and rituximab-EU will be supplied as sterile, preservative-free, non-pyrogenic, single use vials. Rituximab concentrate for solution for infusion will be supplied packaged as blinded supplies in which the external packaging (carton) for both products will appear identical and identified with a unique container number. Each blinded carton will contain 1 vial of study medication. Each carton will be packaged with a tamper-resistant seal. The Sponsor must be notified of any study medication in which the tamper-resistant seal has been broken and this medication should not be used. Further details will be detailed in the Investigational Product Manual.

Each vial of rituximab-Pfizer will contain 500 mg of PF-05280586 in 50 mL clear glass vials. Each vial of rituximab-EU (MabThera) will contain 500 mg of rituximab in 50 mL clear glass vials.

5.3.2. Preparation and Dispensing

Rituximab-Pfizer will be prepared and dispensed in accordance with the European Medicines Authority (EMA) approved labeling for MabThera (rituximab-EU) or the local product label for rituximab.

Only qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents.

5.3.2.1. Rituximab Infusion Preparation

Rituximab (rituximab-Pfizer or rituximab-EU) solutions for infusion will be prepared by a pharmacist designated as participating in this study as an unblinded pharmacist. Unblinded pharmacists will receive study specific training on the obligations of the role and will sign an agreement that will be maintained in the Site Master File. No information concerning patient treatment assignments will be communicated from the unblinded pharmacist to investigators, site study staff, sponsor study staff, or study patients. Rituximab will be administered by intravenous (IV) infusion. Pharmacists should use aseptic technique appropriate to parenteral administration projects. Rituximab vials and prepared solutions should be inspected visually for particulate matter and discoloration prior to administration. Do not use vials if particulates or discoloration are present. Following the Dosage and Administration Instructions, withdraw the necessary amount of rituximab (rituximab-Pfizer or rituximab-EU) and dilute to a final concentration of 1 mg/mL to 4 mg/mL in an infusion bag containing either 0.9% Sodium Chloride, USP, or 5% Dextrose in Water, USP. Gently invert the bag to mix the solution. Do not mix or dilute the study drug product with other drugs. Reference the Dosage and Administration Instructions for further details.

5.3.2.2. Pre-Medication for Rituximab Infusions

All patients should receive premedication with 100 mg IV methylprednisolone or its equivalent prior to rituximab infusion to decrease the incidence rate and severity of acute infusion related reactions. Premedication consisting of an anti-pyretic and an antihistamine (eg, paracetamol [acetaminophen] and diphenhydramine) should be administered before infusion of rituximab. Acute infusion reactions are most often observed during the first infusion of rituximab. Any reduction in dose of premedications during subsequent infusions should be in compliance with local labeling and regulation.

5.3.3. Rituximab Administration

Blinded rituximab (rituximab-Pfizer or rituximab-EU) will be administered by IV infusion using the escalating infusion rate described in the Health Authority approved product label. The rituximab infusion rate must be well controlled to reduce the incidence of serious infusion reactions.

Only qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents.

Rituximab infusions should be administered under close medical supervision and in an environment where full resuscitation facilities are immediately available. Vital signs, including heart rate, seated blood pressure, respiratory rate and oral or tympanic body temperature should be monitored every 30 minutes (± 5 minutes) during the course of the treatment administration or more frequently as necessary.

Rituximab will be administered at a dose of 375 mg/m^2 at Visits 2, 3, 4, and 5 (Days 1, 8, 15, and 22). The body surface area (BSA) for the patient should be calculated using a standard formula and the patient's weight and height. The weight and height at Screening may be used to calculate the BSA for all doses unless the patient has had a clinically significant change in weight. If a patient appears to have a significant change in weight from Screening at a dosing visit, please check his or her weight prior to administering study medication and adjust the dose if there has been a change of more than 10%. The maximum dose of rituximab that can be administered is 1125 mg.

The instructions below provide a summary of guidance provided in the MabThera product labeling, which should also be followed for rituximab-Pfizer; rituximab should be administered according to the local product labeling if it differs from these instructions.

- Day 1 Infusion: Initiate infusion at a rate of 50 mg/hr. After 30 minutes and in the absence of infusion toxicity, increase infusion rate by 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.
- Day 8, 15, and 22 Infusions: Initiate infusion at a rate of 100 mg/hr. After 30 minutes and in the absence of infusion toxicity, increase rate by 100 mg/hr increments at 30-minute intervals, to a maximum of 400 mg/hr.
- Patients should be closely monitored for the onset of cytokine release syndrome. Patients who develop evidence of severe reactions, especially severe dyspnea, bronchospasm or hypoxia should have the infusion interrupted immediately. In all patients, the infusion should not be restarted until complete resolution of all symptoms, and normalization of laboratory values. At this time, the infusion can be initially resumed at not more than one-half the previous rate. If the same severe adverse reactions occur for a second time, the decision to stop the treatment should be seriously considered on a case by case basis.
- Mild to moderate infusion-related reactions usually respond to a reduction in the rate of infusion. The infusion rate may be increased upon improvement of symptoms.
- The patient should be observed post-infusion if necessary based on the investigator's medical judgment.

Medication errors may result, in this study, from the administration or consumption of the wrong product, by the wrong patient, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the medication error case report form (CRF) which is a specific version of the adverse event (AE) page and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving patient exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating patient.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is captured on the medication error version of the AE page and, if applicable, any associated adverse event(s) is captured on an adverse event (AE) CRF page.

5.3.4. Compliance

Study treatment will be administered under the supervision of the investigator and site personnel. Compliance will be monitored by study personnel at the site by using the source documents and the eCRFs. The unblinded site study pharmacist is responsible for drug preparation, the maintenance of accurate and complete dispensing and accountability forms showing the receipt and dispensation of rituximab. The unblinded pharmacist will also be responsible for performing accountability and reconciliation of the investigational products.

5.4. Drug Storage and Drug Accountability

All drug supplies for this study must be stored according to labeled storage conditions. The investigator, or an approved representative (eg, pharmacist), will ensure that all study drug is stored in a secured (locked) area with restricted access, and in accordance with applicable regulatory requirements.

Drug should be stored in accordance with the drug label. Storage conditions stated in the Single Reference Safety Document (SRSD) (ie, Investigator Brochure (IB)) will be superseded by the label storage.

Investigators and site staff are reminded to check temperatures daily (manually or by using alarm systems to alert of any excursions) and ensure that thermometers are working correctly as required for proper storage of investigational products. These include thermometers for refrigerator storage. Any temperature excursions should be reported to the sponsor.

The investigational product(s) must be stored as indicated. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor. Once a deviation is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product.

5.5. Concomitant and Prohibited Medication(s)

The use of concomitant therapy, including prescription and nonprescription drugs, non-drug therapy, and dietary supplements and herbal preparations, is permitted as appropriate to treat adverse events or co-morbid conditions. Patients should not receive long term, high dose steroid treatment during the study. Patients should not receive a live virus vaccine during the study as rituximab treatment will reduce the B lymphocyte count and B lymphocyte recovery may take up to 1 year post-treatment. Patients may be vaccinated with non-live vaccines, although the response rate for these vaccines may be reduced. Patients who receive prohibited steroid medication or a live vaccine do not have to be withdrawn from the study.

Concomitant administration of any other experimental drug or a concomitant chemotherapy, anticancer hormonal therapy, radiotherapy, or immunotherapy is prohibited during study participation. This includes additional doses of rituximab after the initial 4-weekly doses. If a patient requires tumor targeting treatment for FL other than the protocol-defined treatment with rituximab monotherapy, he or she will be considered a treatment failure and should be withdrawn from the study.

6. STUDY PROCEDURES

6.1. Screening (Visit 1 - Study Days -56 to 0)

The following screening procedures will be performed within 56 days prior to the first day of blinded study drug administration (Day 1) unless otherwise stated.

- Informed consent (must be obtained prior to the patient undergoing any study specific procedures and may occur prior to the 56-day screening period as permitted by local regulations or IRB/EC guidelines).
- Confirm diagnosis of Grade 1 – 3a, CD20+ FL and ensure tissue or slides are available for the central pathology reviewer.
- Evaluate lymphoma-related signs and symptoms and ensure the patient is not experiencing B symptoms (fever $>38^{\circ}\text{C}$ for 3 consecutive days, recurrent, drenching night sweats, and unintentional weight loss exceeding 10% body weight in 6 months).
- Ensure the patient is Ann Arbor Stage II, III, or IV ([Appendix 1](#)).
- Collect information for FLIPI and FLIPI2 ([Appendix 2](#)).
- Collection of demographic information.
- Medical history, including prior and current treatments for FL and other medical conditions, history of other significant medical conditions (active or resolved), and concomitant illnesses.
- Prior and current medications.

- Complete physical examination (PE), including examination of major body systems, body weight, and height. The PE must include a thorough assessment of the lymph nodes, spleen, and liver.
- Vital signs, including heart rate, seated blood pressure, respiratory and oral or tympanic body temperature.
- ECOG performance status assessment.
- Laboratory testing, including hematology, blood chemistry, urinalysis, serum β 2-microglobulin, lactate dehydrogenase (LDH), viral disease screening (hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody, and HIV), and testing for circulating lymphoma cells. HIV testing should be conducted unless prohibited by local regulations. Screening laboratory tests must be conducted within 28 days of the first dose of study medication (Day 1). Screening lab tests may be repeated one time to re-evaluate potentially exclusionary values.
- Serum pregnancy test (human chorionic gonadotrophin - hCG) for women of childbearing potential. Female patients with documented history of hysterectomy, bilateral oophorectomy, medically confirmed ovarian failure, or follicle-stimulating hormone (FSH) test demonstrating post-menopausal status are exempted from pregnancy testing.
- 12-lead electrocardiogram (ECG).
- Diagnostic quality [18F]FDG-PET/CT or a CT scan with contrast and a separate [18F]FDG-PET scan. Scans acquired up to 8 weeks prior to Day 1 may be used for Screening provided they are of adequate quality for central imaging review. The quality of all CT scans must be sufficient for accurate anatomical measurement of lymphoma lesions and for central review. PET/CT scans should be performed from the base of the skull to the proximal femurs; CT scans should include the neck, chest, abdomen, and pelvis. Patients for whom IV contrast is medically contraindicated should have an MRI of the neck, abdomen and pelvis and a non-contrast CT of the chest.
- Bone marrow biopsy or aspiration, unless the patient has had a previous bone marrow biopsy or aspiration that was positive for bone marrow involvement (biopsies or aspirations performed up to 12 weeks prior to Day 1 may be used for Screening). Bone marrow aspiration and/or biopsy should be confirmed as adequate for evaluation and interpretation by the Investigator or medically qualified designee.
- Review inclusion/exclusion criteria.
- Record screening visit in IMPALA.

6.2. Study Period

6.2.1. Day 1 Visit (Visit 2)

- Review inclusion/exclusion criteria to ensure patient eligibility.
- Randomization via IMPALA (may be conducted up to 5 business days prior to Day 1). Sponsor confirmation of eligibility must be received prior to randomization.

NOTE: Randomization will be stratified based on low, medium and high risk patients using the Follicular Lymphoma International Prognostic Index 2 (FLIPI2). It is critical that the FLIPI2 is scored correctly and that this information is entered into IMPALA accurately.

- IMPALA study drug assignment (performed by the unblinded pharmacist - may be conducted up to 5 business days prior to Day 1).
- Targeted PE, including body weight. The Targeted PE must include a thorough assessment of the lymph nodes, spleen, and liver.
- Vital signs, including heart rate, seated blood pressure, respiratory rate and oral or tympanic body temperature.
- Laboratory testing, including chemistry, hematology, serum β 2-microglobulin and lactate dehydrogenase (LDH).
- Urine pregnancy test for female patients of childbearing potential.
- Serum PK sampling. One PK sample will be collected within 4 hours prior to the start of the study medication infusion and another sample will be collected within 15 minutes prior to end of study medication infusion. The end of the infusion is the time when the entire dose of study medication has been administered and the 10 minute flush with diluent has been completed.
- CD19+ B-cell count sampling. The CD19+ B-cell sample will be collected within 4 hours prior to the start of the study medication infusion.
- Immunogenicity (ADA/Nab) sampling. The ADA/Nab sample will be collected within 4 hours prior to the start of the study medication infusion.
- IgG and IgM sampling. The IgG and IgM sample will be collected within 4 hours prior to the start of the study medication infusion.
- Evaluate lymphoma-related signs and symptoms, including B symptoms (fever $>38^{\circ}\text{C}$ for 3 consecutive days, recurrent, drenching night sweats, and unintentional weight loss exceeding 10% body weight in 6 months).
- Contraception check.

- Administration of premedications.
- Study drug administration.
- Concomitant medications.
- Adverse events.

6.2.2. Treatment Visits (Visits 3, 4, and 5 - Study Days 8, 15, and 22)

- Targeted PE, including body weight. The Targeted PE must include a thorough assessment of the lymph nodes, liver and spleen.
- Vital signs, including heart rate, seated blood pressure, respiratory rate and oral or tympanic body temperature.
- Serum PK sampling. One PK sample will be collected within 4 hours prior to each infusion. On Day 22 only, an additional PK sample will be collected within 15 minutes prior to end of infusion. The end of the infusion is the time when the entire dose of study medication has been administered and the 10 minute flush with diluent has been completed.
- CD19+ B-cell count sampling.
- Immunogenicity (ADA/Nab) sampling (Visit 4, Day 15 only).
- IgG and IgM sampling.
- Administration of premedications.
- Study drug administration.
- Concomitant medications.
- Contraception check.
- Adverse events.

6.2.3. Follow-up Visits (Visits 6, 7, 8, and 9 – Weeks 5, 13, 26, and 39)

- Evaluate lymphoma-related signs and symptoms, including B symptoms (fever $>38^{\circ}\text{C}$ for 3 consecutive days, recurrent, drenching night sweats, and unintentional weight loss exceeding 10% body weight in 6 months).
- Targeted PE, including body weight. The Targeted PE must include a thorough assessment of the lymph nodes, liver and spleen.

- Vital signs, including heart rate, seated blood pressure, respiratory rate and oral or tympanic body temperature.
- ECOG performance status assessment.
- Laboratory testing, including chemistry, hematology, serum β 2-microglobulin and lactate dehydrogenase (LDH).
- Diagnostic quality [18F]FDG-PET/CT or CT scan with contrast. PET/CT scans should be performed from the base of the skull to the proximal femurs; CT scans should include the neck, chest, abdomen, and pelvis. Patients for whom IV contrast is medically contraindicated should have an MRI of the neck, abdomen and pelvis and a non-contrast CT of the chest.
- For patients with positive PET findings at Screening who have not undergone PET/CT scans at the follow up visits, a second PET scan should be obtained during Follow-Up (Weeks 13-39) or at End of Study/Early Termination (Week 52) when the patient experiences a complete remission based on the investigator's review of the CT scan results. The follow-up PET should be performed within 4 weeks of the contrast enhanced CT.
- Bone marrow biopsy or aspiration for patients with positive findings at Screening who have experienced a complete response based on the Investigator's review of the CT or PET/CT scan. A follow-up bone marrow biopsy or aspiration should be performed once between Week 13 and Week 52 for patients who have bone marrow involvement at Screening at the time when the Investigator determines that the patient has achieved a Complete Remission – the bone marrow biopsy or aspiration should be performed within 4 weeks of the contrast enhanced PET/CT or CT.
- Serum PK sampling.
- CD19+ B-cell count sampling.
- Immunogenicity (ADA/Nab) sampling.
- IgG and IgM sampling.
- Concomitant medications.
- Contraception check.
- Adverse events.

6.2.4. End of Study/Early Termination Visit (Visit 10 - Week 52)

- Evaluate lymphoma-related signs and symptoms, including B symptoms (fever $>38^{\circ}\text{C}$ for 3 consecutive days, recurrent, drenching night sweats, and unintentional weight loss exceeding 10% body weight in 6 months).

- Complete PE, including body weight. The PE must include a thorough assessment of the lymph nodes, liver and spleen.
- Vital signs, including heart rate, seated blood pressure, respiratory and oral or tympanic body temperature.
- ECOG performance status assessment.
- Laboratory testing, including chemistry, hematology, urinalysis, serum β 2-microglobulin, and lactate dehydrogenase (LDH).
- Serum pregnancy test (HCG) for women of childbearing potential.
- 12-lead ECG.
- Diagnostic quality [18F]FDG-PET/CT or CT scan with contrast. PET/CT scans should be performed from the base of the skull to the proximal femurs; CT scans should include the neck, chest, abdomen, and pelvis. Patients for whom IV contrast is medically contraindicated should have an MRI of the neck, abdomen and pelvis and a non-contrast CT of the chest.
- For patients with positive PET findings at Screening who have not undergone PET/CT scans at the follow up visits, a second PET scan should be obtained during Follow-Up (Weeks 13-39) or at End of Study/Early Termination (Week 52) when the patient experiences a complete remission based on the investigator's review of the CT scan results. The follow-up PET should be performed within 4 weeks of the contrast enhanced CT.
- Bone marrow biopsy or aspirate for patients with positive findings at Screening who have experienced a complete response based on the Investigator's review of the CT or PET/CT scan. A follow-up bone marrow biopsy or aspiration should be performed once between Week 13 and Week 52 for patients who have bone marrow involvement at Screening at the time when the Investigator determines that the patient has achieved a Complete Remission – the bone marrow biopsy or aspiration should be performed within 4 weeks of the contrast enhanced PET/CT or CT.
- Serum PK sampling.
- CD19+ B-cell count sampling.
- Immunogenicity (ADA/Nab) sampling.
- IgG and IgM sampling.
- Concomitant medications.
- Contraception check.
- Adverse events.

6.3. Patient Withdrawal

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the patient to comply with the protocol required schedule of study visits or procedures at a given study site.

Patients who cannot receive all four doses of study medication may be withdrawn from treatment, but may remain in the study.

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. All attempts to contact the patient and information received during contact attempts must be documented in the patient's medical record. In any circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the reason for withdrawal, request the patient to return for a final visit, if applicable, and follow up with the patient regarding any unresolved AEs.

Patients who withdraw from the study should have an End of Study (Visit 10 – Week 52) /Early Termination Visit completed if they are not discontinued at a scheduled study visit. If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However it is anticipated that from time to time there may be circumstances, outside of the control of the investigator, that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well being of the patient. When a protocol required test cannot be performed the investigator will document the reason for this and any corrective and preventive actions which he/she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

7.1. Efficacy Assessments

Disease assessments are to be performed as scheduled according to calendar days, regardless of treatment delays resulting from toxicity. Care must be taken in scheduling disease assessments to prevent the introduction of bias based on treatment delays.

Failure to perform any of the required disease assessments will result in the inability to determine disease status for the impacted time point. A series of incomplete disease assessments will result in inability to determine disease response status. Frequently off-schedule or incomplete disease assessments have the potential to weaken the conclusion of this clinical trial.

Assessments are NOT to be scheduled based on the previous imaging timepoint, but rather Day 1 should be used as the baseline when calculating when the on-study tumor assessments are to be performed. Diagnostic quality PET/CT or CT scans should be performed with contrast agents, unless contraindicated for medical reasons. Patients for whom IV contrast is medically contraindicated should have an MRI of the neck, abdomen and pelvis and a non-contrast CT of the chest.

All imaging performed for the study will be forwarded to the central imaging vendor for review and assessment of response for the primary and secondary efficacy assessments. Details of the response assessment procedures are provided in the imaging charter.

Investigators will review the Screening PET/CT or CT scans to determine patient eligibility for the study. Investigators will review the post-treatment PET/CT or CT scans to determine if a Complete Remission (CR) has occurred and to provide appropriate medical care to patients. The Investigator should make the determination of whether a patient has experienced a CR using the revised response criteria for malignant lymphoma (2007)¹¹ – see [Appendix 3](#). If a patient who had PET-avid disease at Screening has experienced a CR based on the Investigator’s review of the CT scan and has not undergone a PET/CT scan, a follow-up PET should be scheduled as soon as feasible. Patients with bone marrow involvement at Screening should have a follow up bone marrow biopsy or aspiration conducted as soon as feasible once the Investigator determines they have experienced a CR. The PET and bone marrow biopsy should be conducted within 4 weeks of the PET/CT or CT. All scans are to be acquired in accordance with the specifications provided in the imaging manuals.

7.2. Safety Assessments

7.2.1. Physical Examination

7.2.1.1. Complete Physical Examination

A standard physical examination will be performed at Screening and End of Study (Week 52) as indicated in the [Schedule of Activities](#). The following parameters and body systems will be examined and any abnormalities described: weight, height (at Screening), general appearance, skin (eg, presence of rash), head, eyes, ears, nose, and throat (HEENT), lungs (auscultation), heart (auscultation for presence of murmurs, gallops, rubs), extremity exam for the presence of peripheral edema, abdominal (palpation and auscultation), and neurologic (mental status and motor and sensory function). The PE must include a thorough assessment of the lymph nodes, liver and spleen. The genitourinary system may be excluded unless there are signs or symptoms involving that system. Any clinically significant changes from the screening visit after initial dosing with study drug should be recorded as adverse events (AEs).

7.2.1.2. Targeted Physical Examination

Targeted physical examinations will be performed as indicated in the [Schedule of Activities](#). Targeted examinations will be guided by signs and symptoms, will include weight and will be consistent with local standard of care. The Targeted PE must include, at a minimum, a

thorough assessment of the lymph nodes, liver and spleen. Any clinically significant changes from the screening visit after initial dosing must be documented and should be recorded as adverse events (AEs).

7.2.2. Vital Signs

Vital signs, including heart rate, blood pressure, respiratory rate and oral or tympanic body temperature, will be measured as detailed in the [Schedule of Activities](#) and in the event of an infusion reaction.

Blood pressure will be measured in the patient's arm and recorded to the nearest mmHg after the patient has been seated quietly for at least 2 minutes. The same arm and position should be used throughout the study, using an appropriate cuff size. When the timing of these measurements coincides with blood collection, the blood pressure and heart rate should be obtained first.

Vital signs are to be obtained prior to each study treatment infusion, every 30 minutes (± 5 minutes) during infusion, at the end of infusion and as clinically indicated. Vital signs should be collected every 30 minutes even if an infusion is interrupted. In the event of hypersensitivity reaction vital signs should be obtained at additional time points until recovery per Investigator judgment.

7.2.3. ECOG Performance Status

ECOG performance status will be graded according to the following definitions in Table 1.

Table 1. ECOG Performance Status Definitions

Grade	ECOG Definition
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

7.2.4. Clinical Laboratory Tests

Blood and urine samples will be collected at the time points identified in the [Schedule of Activities](#). Hematology and blood chemistry tests will include the parameters presented in [Table 2](#). Unscheduled clinical labs may be obtained at any time during the study to assess any perceived safety concerns. All laboratory testing except for urine pregnancy tests will be performed by the central laboratory whenever possible; urine pregnancy tests will be provided by the central lab, but testing will be conducted at the site for female patients of

childbearing potential. Local laboratory testing may be conducted to verify patient eligibility or monitor patient safety if central laboratory results cannot be obtained in a timely fashion. Local laboratory values used to verify eligibility should be entered into the eCRF.

Screening lab tests may be repeated one time to re-evaluate potentially exclusionary values.

Table 2. Required Laboratory Tests

Laboratory Test Panel	Parameters Included
Hematology	Hemoglobin, white blood cell (WBC), count, platelet count, and neutrophils (ANC)
Chemistry	ALT (SGPT), AST (SGOT), alkaline phosphatase, serum sodium, sodium potassium, total calcium (EDTA), total bilirubin, urea nitrogen, creatinine, serum uric acid, and albumin-QT. <i>If drug-induced liver disease is suspected (potential Hy's law cases), in addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/INR, and alkaline phosphatase.</i>
Urinalysis	If abnormal, a microscopic examination of spun sediment will be performed.
Pregnancy Tests	Serum pregnancy test at Screening and End of Study/Early Termination and urine pregnancy test (performed by site personnel) at Day 1 for female patients of childbearing potential
Other Tests	Circulating lymphoma cells and viral disease screen (at Screening), β -2 microglobulin, LDH

Details about the required laboratory testing and sample processing are provided in the Covance Lab Manual.

7.2.5. Viral Disease Screening

Patients will be tested for Human Immunodeficiency Virus (HIV), hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), and hepatitis C antibody (HCVAb) to determine eligibility. Screening for HIV infection should be performed unless prohibited by local regulations.

7.2.6. Pregnancy Testing

For female patients of childbearing potential, a serum pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed at Screening. A urine pregnancy test will be performed on Day 1 prior to dosing. A negative pregnancy result is required before the patient may receive the investigational product. Serum pregnancy tests will also be done whenever one menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study to confirm the patient has not become pregnant during the study. Patients should not be treated with study medication if pregnancy is suspected. In the case of a confirmed positive hCG test, the patient will be withdrawn from treatment, but may remain in the study. Additional pregnancy tests may also be conducted as requested by IRB/IECs or if required by local regulations.

7.2.7. Electrocardiogram

Twelve-lead ECGs should be performed after the patient has rested quietly for at least 10 minutes. End of Treatment ECGs will be compared to Screening ECGs and any clinically significant changes will be recorded as adverse events and evaluated further, as clinically warranted.

7.2.8. Adverse Events

Assessment of adverse events will include type, incidence, severity (graded by the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE], Version 4.03), timing, seriousness, and relatedness.

Baseline tumor-related signs and symptoms will be recorded as adverse events during the trial if they worsen in severity or increase in frequency.

7.3. Pharmacokinetic Assessments

Samples for the determination of serum concentrations of rituximab-Pfizer and rituximab-EU will be collected at the time points specified in the [Schedule of Activities](#). The actual time of each sample collection will be recorded on the source document and CRF. Samples collected within the allowable visit window specified in the Schedule of Activities are acceptable.

Details on sample collection, processing, and shipment will be provided in the central laboratory manual. All samples will be analyzed by the designated analytical laboratory using a validated analytical method in compliance with Pfizer standard operating procedures.

7.4. Immunogenicity Assessments

Blood samples for assessment of ADA and Nab will be collected at time points specified on the [Schedule of Activities](#). Details on sample collection, processing, and shipment are provided in the central laboratory manual. All samples will be analyzed by designated analytical laboratory using a validated analytical method in compliance with Pfizer standard operating procedures.

Analysis of ADA samples will follow a tiered approach of screening, confirmation, and titer determination. Samples that are confirmed positive for ADA will be further tested for neutralizing antibodies using validated neutralizing antibody assays.

7.5. Pharmacodynamic Assessments

The PD of rituximab-Pfizer and rituximab-EU will be evaluated using circulating CD19 positive B-cell counts (surrogate marker for CD20+ B-cells).

Blood samples for circulating CD19+ B-cell counts will be collected according to the [Schedule of Activities](#).

Because rituximab depletes B-cells, circulating levels of IgM and IgG may decrease. Blood samples for IgG and IgM will be collected according to the [Schedule of Activities](#).

For details on obtaining, processing and shipping samples, see the Laboratory Manual. The shipment address and assay lab contact information will be provided to the investigator site prior to initiation of the trial. All samples will be analyzed by a central laboratory using a validated analytical method in compliance with Pfizer standard operating procedures.

7.6. Histopathological Review of Diagnostic Tissue

To be eligible for this trial, patients must have tumor tissue or slides available for a central pathology review. The patient may be enrolled in the study and randomized based on a diagnosis of Grade 1-3a, CD20-positive follicular lymphoma with no elements of high grade or diffuse large B-cell lymphoma documented in a histopathological report that has been reviewed by the Investigator. Tumor tissue blocks or slides will be collected and sent to the central laboratory for standardized evaluation of the diagnosis. The tissue blocks will be returned to the site upon request. The primary analysis for study outcome will be based on diagnosis confirmed by the Investigator. Supportive analyses may consider diagnosis documented during the retrospective evaluation.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the Sponsor, any non-serious adverse event that is determined by the Sponsor to be serious will be reported by the Sponsor as an SAE. To assist in the determination of case seriousness further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last study visit. Serious adverse events occurring to a patient after the active reporting period has ended should be reported to the Sponsor if the investigator becomes aware of them; at a minimum, all serious adverse events that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the Sponsor.

AEs (serious and non-serious) should be recorded on the CRF from the time the patient has taken at least one dose of investigational product through patient's last visit. If a patient begins a new anticancer therapy, the AE reporting period for non-serious AEs ends at the time the new treatment is started. Death must be reported if it occurs during the SAE reporting period after the last dose of investigational product, irrespective of any intervening treatment.

8.3. Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation patient administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure;
- Worsening of signs and symptoms of the malignancy under study should be reported as AEs in the appropriate section of the CRF. Disease progression assessed by

measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

8.4. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

8.5. Serious Adverse Events

An SAE is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an AE and as an SAE with CTCAE Grade 5 (see Section on [Severity Assessment](#)).

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize

the patient or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.5.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections and will be handled as SAEs in the safety database (see Section on [SAE Reporting Requirements](#)).

8.5.2. Potential Cases of Drug-Induced Liver Injury

Liver function tests (LFTs) are not required as a routine safety monitoring procedure in this study. However, should an investigator deem it necessary to run LFTs because of a clinical sign/symptom presentation in a patient, such LFT results should be handled and followed up as described below.

Abnormal values in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the patient's individual baseline values and underlying conditions. Patients who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Patients with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥ 3 times the upper limit of normal (X ULN) concurrent with a total bilirubin value ≥ 2 X ULN with no evidence of hemolysis and an alkaline phosphatase value ≤ 2 X ULN or not available;
- For patients with preexisting ALT **OR** AST **OR** total bilirubin values above the upper limit of normal, the following threshold values should be used in the definition mentioned above:
- For patients with pre-existing AST or ALT baseline values above the normal range: AST or ALT values ≥ 2 times the baseline values and ≥ 3 X ULN, or ≥ 8 X ULN (whichever is smaller).
- Concurrent with

- For patients with pre-existing values of total bilirubin above the normal range: Total bilirubin increased from baseline by an amount of at least one time the upper limit of normal **or** if the value reaches ≥ 3 times the upper limit of normal (whichever is smaller).

The patient should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment. In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/ international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for LFT abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's Law cases should be reported as SAEs.

8.6. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for work-up of persistent pre-treatment lab abnormality);
- Social admission (eg, patient has no place to sleep);
- Administrative admission (eg, for yearly physical exam);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Pre-planned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual patient;
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

8.7. Severity Assessment

The investigator will describe the maximum intensity of the AE. The US National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, Version 4.03 (CTCAEv4.03) will be used to grade severity. A printable version of these criteria can be found at http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.

GRADE	CLINICAL DESCRIPTION OF SEVERITY
0	No Change from Normal or Reference Range (This grade is not included in the Version 4.03 CTCAE document but may be used in certain circumstances.)
1	MILD Adverse Event
2	MODERATE Adverse Event
3	SEVERE Adverse Event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO Adverse Event

The NCI CTCAE severity grades for an infusion related reaction should be used to grade the severity of adverse events that the investigator deems infusion-related reaction (allergic or hypersensitivity reactions):

GRADE	CLINICAL DESCRIPTION OF SEVERITY FOR IRRs
1	Mild transient reaction; infusion interruption not indicated; intervention not indicated
2	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for <=24 hours
3	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae
4	Life-threatening consequences; urgent intervention indicated
5	Death

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with patient's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.8. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the Sponsor (see Section on [Reporting Requirements](#)). If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

In addition, if the investigator determines an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

8.9. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes, or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a study patient or study patient's partner becomes or is found to be pregnant during the study patient's treatment with the investigational product, the investigator must submit this information to the Pfizer Drug Safety Unit on a Serious Adverse Event (SAE) Report Form and Exposure During Pregnancy supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a patient reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information about the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer of the outcome as a follow up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as serious adverse events when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the exposure during pregnancy may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study patient with the Pregnant Partner Release of Information Form to deliver to his partner. The Investigator must document in the source

documents that the patient was given the Pregnant Partner Release of Information Form to provide to his partner.

8.10. Occupational Exposure

An occupational exposure occurs when during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an adverse event.

An occupational exposure is reported to the drug safety unit within 24 hours of the Investigator's awareness, using the SAE Report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a patient enrolled in the study, the information is not reported on a Case Report Form (CRF), however a copy of the completed SAE Report form is maintained in the investigator site file.

8.11. Withdrawal Due to Adverse Events (See Also the Section on [Patient Withdrawal](#))

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a patient withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.12. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study patient. In addition, each study patient will be questioned about AEs.

8.13. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

8.13.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy, exposure via breastfeeding and occupational exposure cases.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study patient initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines and/or illnesses must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

8.13.2. Non-Serious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

8.13.3. Sponsor's Reporting Requirements to Regulatory Authorities

Adverse event reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be maintained by the Sponsor. The SAP may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

9.1. Sample Size Determination

The primary hypothesis to be tested in this study is that the difference between the ORR of rituximab-Pfizer versus that of rituximab-EU is within a pre-specified margin of -16% to 16% (the margin derivation is described below). A sample size of approximately 394 patients (~197 per treatment arm) provides approximately 93% power for achieving equivalence under the specified margin with 2.5% type I error rate assuming an ORR of 77% in both treatment arms.

Pfizer conducted an extensive, systematic literature search for rituximab and FL. The Ardeshta⁷ study was the only randomized trial which compared the treatment of rituximab alone with the treatment of “watchful waiting” (WW). In this study, at Month 7 the response rate to rituximab therapy (weekly for 4 weeks) was estimated to be 77% and the response rate in the WW arm was estimated to be 6%. The difference (rituximab - WW) was estimated to be 71% with the 95% confidence interval of (60%, 79%). Based on these results, the proposed margin of (-16%, 16%) will preserve at least 73% efficacy based on the lower bound of 95% CI in the ORR difference (rituximab-WW) as seen in the Ardeshta study.⁷

9.2. Analysis Population

9.2.1. Intent-to-Treat Population

The Intent-to-Treat (ITT) Population is defined as all patients who are randomized to study treatment. The ITT population will be used as the primary efficacy analysis population.

9.2.2. Per-Protocol Population

The Per-Protocol (PP) Population is defined as all randomized patients who receive at least one dose of study treatment, have measurable disease at baseline as confirmed by central review, and have no important protocol deviations that would impact the study outcome significantly, as determined by blinded medical review. The PP population will be used for sensitivity analyses of the efficacy and biomarker analyses. All decisions to exclude patients from the PP population will be made prior to database release.

9.2.3. Safety Population

The safety population is defined as all patients who received at least one dose of study treatment. The safety population will be used for the safety analyses including AE, concomitant medication, laboratory tests, vital signs, ADA and neutralizing antibody analyses, etc.

9.3. Efficacy Analysis

9.3.1. Analysis of Primary Endpoint

The primary efficacy endpoint of the study is ORR defined as the percent of patients within each treatment group that achieved Complete Remission (CR) or Partial Remission (PR) at the end of Week 26.

The following primary hypothesis will be tested for ORR in order to show that rituximab-Pfizer is equivalent to rituximab-EU:

TEST 1: $H_{0c}: \theta_1 - \theta_2 \geq D_{ub}$ vs. $H_{1c}: \theta_1 - \theta_2 < D_{ub}$

TEST 2: $H_{0d}: \theta_1 - \theta_2 \leq D_{lb}$ vs. $H_{1d}: \theta_1 - \theta_2 > D_{lb}$

Where θ_1 is the ORR at Week 26 for patients randomized to rituximab-Pfizer, θ_2 is the ORR at Week 26 for patients randomized to rituximab-EU, D_{ub} is the largest acceptable risk difference for equivalence, and D_{lb} is the smallest acceptable risk difference for equivalence. In this study, $D_{ub}=16\%$ and $D_{lb}=-16\%$.

According to a requirement from the regulatory authority in Japan, an additional analysis will be conducted to test equivalence using $D_{ub} = 14.9\%$ and $D_{lb} = -14.9\%$ if equivalence is established with the margins of $D_{ub}=16\%$ and $D_{lb}=-16\%$.

The stratified Miettinen and Nurminen method¹³ will be used to obtain the estimated difference (rituximab-Pfizer minus rituximab-EU) and its 95% confidence interval.

The study will meet the primary objective if the 95% confidence interval for the ORR difference (rituximab-Pfizer minus rituximab-EU) is within the pre-specified margin of (-16%, 16%). For the regulatory authority in Japan, equivalence will be demonstrated if the 95% confidence interval for the ORR difference (rituximab-Pfizer minus rituximab-EU) is within the margin of (-14.9%, 14.9%).

Descriptive statistics (frequency and percentage) for CR, PR, and ORR will be presented by treatment group. The 95% confidence intervals of these response rates will be constructed. Other details will be described in the Statistical Analysis Plan (SAP).

9.3.2. Analysis of Other Efficacy Endpoints

Other efficacy endpoints include:

- Time to Treatment Failure (TTF).
- Progression-Free Survival (PFS).
- Complete Remission (CR) rate at Week 26.
- Duration of response.
- Overall survival.

The analyses for these endpoints are briefly described below. Details of planned analyses for these efficacy endpoints will be described in the SAP.

9.3.2.1. Time to Treatment Failure

Time to Treatment Failure is defined as the time from date of randomization to discontinuation from study for any reason, including disease progression, treatment toxicity, patient preference, or death. A stratified log-rank test will be used to compare the TTF curves between the two treatment groups. TTF will also be summarized using Kaplan-Meier survival curves. The Kaplan-Meier survival estimates, together with the number of patients, percentage of patients to experience the event, and the number and percentage of patients censored will be summarized in a table by treatment group.

9.3.2.2. Progression Free Survival

Progression-Free Survival (PFS) is defined as the time from date of randomization to first progression of disease (PD) or death due to any cause in the absence of documented PD. Censoring for the PFS endpoint will be assigned on the date of the last tumor assessment if no assessment of tumor progression is identified and the patient does not die while on study. Progression will be based on central review. Patients lacking of an evaluation of disease after randomization will have their PFS time censored on the date of randomization with duration of 1 day.

A stratified log-rank test will be used to compare PFS curves between the two treatment groups. PFS will also be summarized using the Kaplan-Meier method. The Kaplan-Meier estimates for the 1-y PFS rates and the 2-sided 95% confidence interval of the rates using the Greenwood's formula will be reported.

9.3.2.3. Complete Remission at Week 26

Complete Remission (CR) is defined as per the revised response criteria for malignant lymphoma.⁶ CR rate will be summarized by treatment group and visit. CR will be assessed by central review based on scans done at Week 26. CR will be analyzed in a similar fashion as for ORR.

9.3.2.4. Duration of Response

Duration of Response (DOR) is defined as the time from date of the first documentation of overall response (CR or PR) to the first documentation of progressive disease (PD) or to death due to any cause in the absence of documented PD. Censoring for the DOR endpoint will be assigned on the date of the last tumor assessment if no assessment of tumor progression is identified and the patient does not die while on study. DOR will only be calculated for the subgroup of patients who have a response and who have measurable disease at baseline and at least 1 post baseline response assessment. A stratified log-rank test will be used to compare the treatment groups with respect to DOR at a 2-sided alpha level of 0.05. DOR will also be summarized using Kaplan-Meier survival curves. The Kaplan-Meier survival estimates, together with the number of patients, percentage of patients to experience the event, and the number and percentage of patients censored will be summarized in a table by treatment group.

9.3.2.5. Overall Survival

Time to death is defined as the time from date of randomization to death due to any cause. Patients will be censored for this endpoint on the date of the last tumor assessment if they do not die at that time. A stratified log-rank test will be used to compare the overall survival (OS) curves between the two treatment groups. Overall survival will also be summarized using the Kaplan-Meier method. The Kaplan-Meier estimates for the 1-y OS rates and the 2-sided 95% confidence interval of the rates using the Greenwood's formula will be reported.

9.4. Safety Analysis

All patients treated with at least one dose of study treatment will be included in the safety analyses. Adverse events will be classified using the medical dictionary for regulatory activities (MedDRA) classification system. The severity of adverse events will be graded according to the NCI CTCAE version 4.03 whenever possible.

Safety data will be evaluated by the incidence of AEs, severity and type of AEs, and by changes from baseline in the patient's vital signs, weight, and clinical laboratory results using the safety population. Exposure to the study drug regimen and reasons for discontinuation will be tabulated. Collected prior and concomitant medications will also be listed and summarized.

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Details of the safety analyses will be described in the Statistical Analysis Plan (SAP).

9.5. Pharmacokinetics, Biomarkers and Immunogenicity

9.5.1. Pharmacokinetics Analysis

The drug concentration-time data will be summarized by descriptive statistics (mean, standard deviation, median, minimum, and maximum) according to treatment.

Population PK assessment will be conducted with the drug concentration-time data using the nonlinear mixed effect modeling approach in accordance with regulatory guidances. All patients from the PP population who are treated with rituximab-Pfizer or rituximab-EU and provide at least one post-dose drug concentration measurement will be included in the population PK analysis. The population PK analysis will estimate typical value and variability for parameters including half-life ($t_{1/2}$), clearance (CL) and volume of distribution (Vd). Also, the influence of selected potential covariates on the PK parameters will be explored; the potential covariates to be explored will include drug product, selected demographics (eg, body weight, sex, age), and ADA status.

The detailed procedures for the population PK analysis, including the model implementation and evaluation, will be described prospectively in the Population Modeling Analysis Plan (PMAP). The results of the analysis will be summarized in a Population Modeling and Analysis Report (PMAR), separate from the clinical study report of this study.

9.5.2. Biomarker Analysis

Summary statistics by treatment and visit will be provided for biomarkers, including CD19-positive B-cell counts, IgM and IgG, etc. Mean change (or percent change) from baseline will be also summarized by treatment and visit and presented in tabular form and/or graphically.

9.5.3. Immunogenicity

For the immunogenicity data, the percentage of patients with positive ADA and neutralizing antibodies will be summarized for each treatment. For patients with positive ADA, the magnitude (titer), time of onset, and duration of ADA response will also be described, if data permit. In addition, efforts will be made, as appropriate, to examine possible correlations of the ADA response with clinical data on the PK, safety and/or efficacy of each product. Because the observed incidence of ADA is highly dependent on multiple factors including the assays used for ADA detection, timing of sample collection and immune status of the patients, the incidence of ADA observed in the planned study may differ from the incidence reported in historical clinical trials.

9.6. Other Endpoints

Demographic and baseline characteristics such as patient age, sex, height, weight, ethnicity, prior therapy, medical history, ECOG performance status and FLIPI and FLIPI2 risk classification will be tabulated and summarized using descriptive statistics. Relationships between baseline patient characteristics and study outcome variables will be explored with appropriate techniques.

Study drug administration will be described in terms of the total number of cycles administered, the median (range) of cycles administered, dose intensity, and reasons for the deviations from planned therapy.

9.7. Interim Analysis

There will be no interim analysis in this study.

9.8. External Data Monitoring Committee

Safety monitoring will be conducted throughout the study by the Pfizer study team. In addition, this study will use an External Data Monitoring Committee (E-DMC).

The E-DMC will be a 3-member panel of external experts that will meet at approximate 3-month intervals throughout the course of the study unless safety concerns requiring their attention arise earlier. An E-DMC liaison will be appointed; this is an individual who represents Pfizer to coordinate communications and facilitates access to Pfizer's resources, but is not involved in the study design, study management, site management, data accrual, or study analysis. The SAP will outline plans for data review. An E-DMC charter will outline the operating procedures of the committee, including a specific description of the scope of their responsibilities, and a communication plan. Records of E-DMC meetings, interactions with Pfizer contacts, assessments and recommendations and materials reviewed will be maintained and kept proprietary and confidential by the E-DMC.

The E-DMC will be responsible for ongoing monitoring of the safety of patients in the study according to the Charter. The recommendations made by the E-DMC to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data which are not endpoints, to regulatory authorities, as appropriate. In this instance, such disease-related efficacy endpoints are not reported individually as SAEs.

The E-DMC will be responsible for the periodic review of accumulating safety data. The E-DMC will advise the Sponsor regarding the safety of patients enrolled in the study.

Additionally, significant findings observed by Study Team will be communicated to the E-DMC for further review and advice.

10. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Pfizer or its agent will conduct periodic monitoring visits to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs is accurate. The

investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be patient to review by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic / original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs, source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's patient chart. In these cases data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator's site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be

retained by the investigator according to International Conference on Harmonisation (ICH), local regulations, or as specified in the Clinical Study Agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the investigator must notify the IRB/IEC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 1996 & 2008).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

12.3. Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws.

Patient names, initials, address, birth date and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer in order to de-identify the trial patient. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data.

The informed consent document must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The informed consent document(s) used during the informed consent process must be reviewed by the sponsor, approved by the IRB/IEC before use, and available for inspection.

The investigator must ensure that each study patient, or his/her legal representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each patient or the patient's legal representative before any study-specific activity is performed. The investigator will retain the original of each patient's signed consent document.

12.4. Patient Recruitment

Patient recruitment efforts are not required for this study because the indication is follicular lymphoma and patients with follicular lymphoma are usually invited by their healthcare professional to participate. However, for those sites that think advertisements are useful, advertisements approved by ethics committees and investigator databases may be used as recruitment procedures.

12.5. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable Competent Authority in any area of the World, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member

End of Trial in a Member State of the European Union is defined as the time at which it is deemed that sufficient patients have been recruited and completed the study as stated in the regulatory application (ie, Clinical Trial Application (CTA)) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

13.2. End of Trial in all Participating Countries

End of Trial in all participating countries is defined as all patients have been followed for 12 months unless lost to follow-up or the patient has died. This is the Last Patient Last Visit plus the time it takes for the Investigator to review all results from that visit. For the purposes of analysis, the study will be unblinded to the Sponsor (but not Investigators or

patients) once all patients have reached the primary endpoint and the database is locked through the end of Week 26.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of PF-05280586 at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating patients and the hospital pharmacy (if applicable) within 14 calendar days. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies conducted in patients that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

Primary Completion Date is defined as the date that the final patient was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated.

[EudraCT](#)

Pfizer posts EU Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer has no objection to publication by Investigator of any information collected or generated by Investigator, whether or not the results are favorable to the Investigational Drug. However, to ensure against inadvertent disclosure of Confidential Information or unprotected Inventions, Investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

Investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, Investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

Investigator will, on request, remove any previously undisclosed Confidential Information (other than the Study results themselves) before disclosure.

If the Study is part of a multi-centre study, Investigator agrees that the first publication is to be a joint publication covering all centers. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the Study at all participating sites, Investigator is free to publish separately, patient to the other requirements of this Section.

For all publications relating to the Study, Institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, <http://www.icmje.org/index.html#authorship>, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the Clinical Study Agreement between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.

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Appendix 1. Ann Arbor Staging System

ANN ARBOR STAGING SYSTEM

Stage	Area of involvement
I	Single lymph node group
II	Multiple lymph node groups on same side of diaphragm
III	Multiple lymph node groups on both sides of diaphragm
IV	Multiple extranodal sites or lymph nodes and extranodal disease

Appendix 2. Follicular Lymphoma International Prognostic Index (FLIPI)

FOLLICULAR LYMPHOMA INTERNATIONAL PROGNOSTIC INDEX (FLIPI)

Parameter	Adverse factors
Age	>60 years
Ann Arbor stage	III–IV
Hemoglobin level	<120 g/L
Serum lactate dehydrogenase (LDH) level	Above upper limit of normal
Number of nodal areas involved	>4

Risk group	Number of adverse factors
Low risk	0–1
Intermediate risk	2
High risk	≥3

FOLLICULAR LYMPHOMA INTERNATIONAL PROGNOSTIC INDEX 2 (FLIPI2)

Parameter	Adverse factors
Age	>60 years
Hemoglobin level	<120 g/L
β2-microglobulin level	Above upper limit of normal
Longest diameter of largest involved node	>6 cm
Bone marrow involvement	Present

Risk group	Number of adverse factors
Low risk	0
Intermediate risk	1–2
High risk	3–5

Appendix 3. Revised Response Criteria for Malignant Lymphoma (2007)

Complete Remission

- Complete disappearance of all detectable evidence of disease
- All nodal index lesions must have regressed to normal size
- All splenic and hepatic nodules and other extranodal sites of disease resolved
- No new sites of disease should be observed