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Regeneron Pharmaceuticals, Inc.

Clinical Study Protocol

A PHASE 3, OPEN-LABEL, RANDOMIZED STUDY TO COMPARE THE EFFICACY AND SAFETY OF ODRONEXTAMAB (REGN1979), AN ANTI-CD20 X ANTI-CD3 BISPECIFIC ANTIBODY, VERSUS INVESTIGATOR'S CHOICE IN PREVIOUSLY UNTREATED PARTICIPANTS WITH FOLLICULAR LYMPHOMA (OLYMPIA-1)

Compound:	REGN1979 (odronextamab)
Study Name:	OLYMPIA-1
Clinical Phase:	3
Protocol Number:	R1979-HM-2298
Protocol Version:	R1979-HM-2298 Amendment 1
Global Amendment 1 Date of Issue	*See appended electronic signature page*
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AMENDMENT HISTORY

Amendment 1

The purpose of this amendment is to address health authority (HA) feedback.

Description of Change	Brief Rationale	Section # and Name
Note that SC rituximab dose will be 1,400 mg/ 23,400 units hyaluronidase human, on day 1 of each cycle.	For specification of SC dosing	• Synopsis (Treatments) • Table 9 Study Interventions Administered • Section 8.1.2.1 Dose and Administration
Clarified language for DLT exception, if at the same grade ≥7 days, by specifying the liver enzymes (AST and ALT) and including clinical CRS or IRR as context	For alignment across odronextamab phase 3 studies	• Section 6.1.3 Dose-Limiting Toxicities
Provided the operating characteristics for the updated non-binding conditional probability criteria to assess the potential harm in OS	To address HA feedback	• Clinical Study Protocol Synopsis: Statistical Plan, Interim Analysis • Section 6.2 Planned Interim Analysis • Section 11.2.2 Part 2 (Randomized Phase) • Section 11.5 Interim Analysis • Table 31 Number of Events and Information Fractions (IF*) at Each Look (new) • Table 32 Operating Characteristics of Prob (HR <1 Observed Data) <20% for Assessing the Potential for Harm in OS (new)
Clarified the measures that will be taken to mitigate potential bias in study conduct.	To mitigate potential bias in study conduct	• Section 8.6 Blinding
Modification to statement regarding PK sample collection	To clarify the importance of PK sample collection during dose delays prior to treatment resumption.	Section 9.1.3 Changes to the Schedule of Events/Study Procedures in Case of Dose Modification
Added option to substitute prednisolone for prednisone in CHOP/CVP chemotherapy	To accommodate equivalent medication use in ex-US regions	• Clinical Study Protocol Synopsis: Treatment(s) • Section 3.2.2 Other Drugs used in R1979-HM-2298 and the Latest Scientific Findings for Reference Safety Information • Table 11 CHOP/CVP and Bendamustine Dose • Table 9 Study Interventions Administered Applied throughout protocol as relevant
Updated the secondary objectives and endpoints to include overall survival (OS) as a key secondary endpoint for Part 2 and included 3 analyses of OS to evaluate any potential for harm and futility	To address HA feedback	• Clinical Study Protocol Synopsis: Objectives • Clinical Study Protocol Synopsis: Treatment(s) • Section 3.2.2 Other Drugs used in R1979-HM-2298 and the Latest Scientific Findings for Reference Safety Information • Table 2 Study Objectives Part 2 (Randomized Phase) • Section 11.4.3.2 Key Secondary Efficacy Analyses • Section 11.4.4 Control of Multiplicity

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Added clarification that at least 20 participants will be treated at the lower dose level if dose is de-escalated, and updated the sample size in Part 1.	To address HA feedback	• Clinical Study Protocol Synopsis: Study Design, Population • Figure 1 Study Flow Diagram • Section 6.1.1.2 Part 1: Safety Run-in • Figure 2 Participant Flow Diagram (Part 1: Safety Run-In) • Figure 3 Participant Flow Diagram (Part 2: Randomized Phase 3) • Section 6.1.2 Description of Dose De-escalation • Section 7.1 Number of Participants Planned • Section 11.2.1 Part 1 (Safety Run-In) • Table 29 Binomial Probability to Observe 1 or More Events for a Given Population Safety Event Rate
Changed recommended dose "Action" to escalate if DLT rate ≤0.221	Clarification of decision rule in line with DLT target	• Table 5 Decision Rule at the Current Dose Level with Target DLT Rate 28%
Extended DLT observation period to include at least 2 full doses of odronextamab.	To address HA feedback	• Section 6.1.3 Dose-Limiting Toxicities
Added a new section describing the study pausing rules for Part 1 and clarified that IDMC will monitor events in Part 2 to assess benefit/risk during the course of the study	To address HA feedback	• Section 6.1.4 Study Pausing Rules for Part 1 and Part 2 (new) • Table 6: Stopping Boundaries to Pause Enrollment for Grade 4 CRS or Treatment-Related Grade 4 ICAN (new) • Table 7: Stopping Boundaries to Pause Enrollment for Treatment-Related, Life-threatening, Non-hematologic AEs (new) Table 8: Stopping Boundaries to Pause Enrollment for Treatment-Related Fatal Events (new) • Section 6.3.2 Independent Data Monitoring Committee
Clarified age-related inclusion criteria	To address international issues	• Section 7.2 Inclusion Criteria #5, #9
Added clarification to that cycle 1 to cycle 6 consists of 21 days.	To address HA feedback	• Section 8.1.1 Odronextamab Dose and Administration
Revised guidelines on odronextamab treatment resumption to include guidelines for all dose delay scenarios per cycle, day of cycle, and last dose administered, for dose levels 1 and -1	To address HA feedback to present odronextamab treatment resumption recommendations for each dose and dosing schedule separately	• Section 8.3.1.2 Treatment Resumption Following Odronextamab Dose Interruption • Table 13 Guidelines on Odronextamab Treatment Resumption for Dose Level 1 Table 14 Guidelines on Odronextamab Treatment Resumption for Dose Level -1 (new)
Clarified that odronextamab should be discontinued due to grade 4 life-threatening non-hematological toxicities with the exception of clinically insignificant lab abnormalities that resolve with supportive care	To address HA feedback	• Table 12 Guidance on Odronextamab Dosing for Hematologic and Non- Hematologic Toxicities (Other than CRS, IRR, and TLS) • Section 8.3.3.1 Reasons for Permanent Discontinuation of Study Drug

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Revised instruction for prophylaxis for *Pneumocystis jirovecii* pneumonia; ie, added that it is mandatory and that the duration is to be determined by the treating physician	To ensure mitigation of the risk of infections due to additional immunosuppression from corticosteroid use and B-cell depletion and for flexibility	• Section 8.4.5 B-Cell Depletion and Infection Prophylaxis • Section 8.8.2 Permitted Medications and Procedures
Revised text on blinding of study team members and independent central efficacy reviewers	To clarify and differentiate blinding to treatment assigned and treatment received	• Section 8.6 Blinding
Additional language regarding the monitoring of concomitant CYP450 substrates in the initial week of dosing has been included	To address HA feedback	• Section 8.8 Concomitant Medications and Procedures
Added 2-sided alpha spending of 0.0001 for the interim futility analysis	To address HA feedback	• Clinical Study Protocol Synopsis: Justification of Sample Size • Section 11.2.2 Part 2 (Randomized Phase) • Section 11.4.4 Control of Multiplicity
Added information on expected OS data maturity and the time of PFS, interim, primary, and end of study analyses	To address HA feedback	• Section 11.2.2 Part 2 (Randomized Phase)
Subgroup analyses were further defined.	To address HA feedback	• Section 11.4.3.1 Primary Efficacy Analysis
Updated interim efficacy analysis to only include 1 interim efficacy analysis for PFS.	To address HA feedback	• Clinical Study Protocol Synopsis: Interim Analysis • Section 6.2 Planned Interim Analysis • Section 11.5 Interim Analysis
Removed instructions for classification, monitoring, and diagnosis of tumor lysis syndrome	Tumor lysis syndrome is an uncommon finding in a slow growing malignancy such as FL; participants at risk for TLS will be closely monitored as deemed necessary by the investigator.	• Section 8.4.4 Tumor Lysis Syndrome • Table 21 Tumor Lysis Syndrome Risk Classification and Monitoring (table removed) • Table 22 Diagnosis of Laboratory and Clinical Tumor Lysis Syndrome*(table removed)
Added vital signs collection at C1D2 and C1D16	To monitor patients during step up dosing.	• Table 23 Schedule of Events for Odronextamab Monotherapy Arm
Pregnancy test moved from cycle 6 day 8 to cycle 6 day 15	To perform the test on a clinic visit day.	• Table 23 Schedule of Events for Odronextamab Monotherapy Arm
CT or MRI added to 90 day post last-dosing follow-up	To increase availability of imaging data	• Table 24 Schedule of Events for Odronextamab Arm – Follow-Up Period
Additional PK sample collections added	Additional samples collected to improve PK assessments	• Table 27 Schedule of Events: Detailed Sample Collection Timepoints for Pharmacokinetics, Immunogenicity, and Biomarkers
Minor editorial/administrative changes made throughout protocol also corrected N and change to ECOG 0-2 (Figures 1-3 only)	For clarification purposes	• Section 8.4.2 Infusion-Related Reactions (IRRs) and Cytokine Release Syndrome (CRS). • Section 8.4.3 Central Nervous System Toxicity (ICANS) • Section 10.2.2 Events that Require Expedited Reporting to Sponsor • Figure 1 Study Flow,

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		• Figure 2 Participant Flow Part 1 • Figure 3 Participant Flow Part 2

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
BMA/BMx	Bone marrow aspirate/ Bone marrow biopsy
B-NHL	B-cell non-Hodgkin lymphoma
BR	Bendamustine + rituximab
BTK	Bruton's tyrosine kinase
BUN	Blood urea nitrogen
CHOP	Cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone
CI	Confidence interval
CMH	Cochran-Mantel–Haenszel test
CMV	Cytomegalovirus
CNS	Central nervous system
CR	Complete response
CR30	Complete response at 30 months
CRF	Case report form (electronic or paper)
CRO	Contract research organization
CRP	C-reactive protein
CRS	Cytokine release syndrome
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
CVP	Cyclophosphamide, vincristine, and prednisone/prednisolone
DCR	Disease control rate
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose-limiting toxicity
DOR	Duration of response
DUICT	Drugs used in clinical trial
EC	Ethics committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture

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EFS	Event free survival
EOI	End of infusion
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EQ-5D-5L	EuroQoL 5 Dimensions 5 Levels
FACT-G	Functional Assessment of Cancer - General
FACT-Lym	Functional Assessment of Cancer Therapy–Lymphoma
FAS	Full analysis set
FBR	Future biomedical research
FDA	Food and Drug Administration
FDG-PET	^{18}F-fluorodeoxyglucose-positron emission tomography
FL	Follicular lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
FWER	Family-wise error rate
GCP	Good Clinical Practice
G-CSF	Granulocyte colony stimulating factor
GP-5	Global Population item 5
GTD	Greatest transverse diameter
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQoL	Health related quality of life
ICANS	Immune effector cell associated neurotoxicity syndrome
ICE	Immune-Effector Cell-Associated Encephalopathy
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent data monitoring committee
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IRB	Institutional Review Board
IRR	Infusion-related reaction
ITT	Intent-to-treat
IV	Intravenous
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein

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MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed effect model repeated measures
MRD	Measurable residual disease
MUGA	Multigated acquisition
NAb	Neutralizing antibody
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NHL	Non-Hodgkin lymphoma
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PD-1	Programmed death receptor -1
PE	Physical exam
PFS	Progression-free survival
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PJP	*Pneumocystis jirovecii* pneumonia
PK	Pharmacokinetics
PR	Partial response
PRO	Patient reported outcome
PT	Preferred term
QW	Once every week
Q2W	Once every 2 weeks
Q4W	Once every 4 weeks
Q8W	Once every 8 weeks
R-CHOP	Rituximab in combination with chemotherapy – cyclophosphamide, doxorubicin, vincristine, prednisone/prednisolone
R-CVP	Rituximab in combination with chemotherapy – cyclophosphamide, vincristine, prednisone/prednisolone
R/R	Relapsed/recurrent
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SD	Stable disease
SmPC	Summary of product characteristics

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SOC	System organ class
SSC	Scientific Steering Committee
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TLS	Tumor lysis syndrome
TTNT	Time to next anti-lymphoma treatment
WBC	White blood cell
WOCBP	Women of childbearing potential

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CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Phase 3, Open-label, Randomized Study to Compare the Efficacy and Safety of Odronextamab (REGN1979), an Anti-CD20 X Anti-CD3 Bispecific Antibody, Versus Investigator's Choice in Previously Untreated Participants with Follicular Lymphoma (OLYMPIA-1)
Short Title	Phase 3, open-label, randomized study comparing odronextamab versus investigator's choice in first line FL
Site Location(s)	Approximately 200 sites globally
Objective(s)	**Part 1:** **Primary objective**: Assess the safety, tolerability, and dose-limiting toxicities (DLTs) of odronextamab in participants with previously untreated follicular lymphoma (FL) **Secondary objectives:** • To characterize the pharmacokinetics (PK) of odronextamab • To assess the immunogenicity of odronextamab • To evaluate the preliminary anti-tumor activity of odronextamab **Part 2:** **Primary objective:** To compare the efficacy of odronextamab versus investigator's choice in participants with previously untreated FL as measured by complete response at 30 months (CR30) per independent central review **Key secondary objectives:** • To compare efficacy per independent central review between odronextamab monotherapy and investigator's choice chemotherapy as measured by: o Progression free survival (PFS) o Event free survival (EFS) • To compare the efficacy of odronextamab monotherapy versus investigator's choice chemotherapy as measured by CR30 per investigator • To evaluate the treatment effects on patient-reported physical function between odronextamab monotherapy and investigator's choice chemotherapy utilizing European Organisation for Research

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	and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30) • To compare the efficacy of odronextamab monotherapy versus investigator's choice chemotherapy as measured by overall survival (OS) **Secondary objectives**: • To assess additional measures of efficacy of odronextamab compared to investigator's choice chemotherapy • To evaluate safety and tolerability of odronextamab compared to investigator's choice chemotherapy • To evaluate the pharmacokinetic (PK) of odronextamab • To assess the immunogenicity of odronextamab • To evaluate the impact of odronextamab compared to investigator's choice therapy on patient-reported outcomes (PROs), including health related quality of life (HRQoL), as measured by EORTC-QLQ-C30, Functional Assessment of Cancer Therapy–Lymphoma (FACT-LymS), Patient Global Impression of Severity (PGIS), Patient Global Impression of Change (PGIC), and EuroQoL 5 Dimensions 5 Levels (EQ-5D-5L) • To evaluate patient-reported overall impact of treatment toxicity by the GP5 item of the validated Functional Assessment of Cancer- General (FACT-G) questionnaire
Study Design	This is an open-label, multicenter, randomized phase 3 study to compare the efficacy and safety of odronextamab to investigator's choice of chemotherapy for treatment of participants with untreated FL. In Part 1 (Safety Run-in), the intended dose of odronextamab monotherapy to carry forward to Part 2 (Randomized Phase) will be tested to assess safety. The efficacy and safety of odronextamab will be evaluated in Part 2, compared with investigator's choice of chemotherapy. **Part 1:** A minimum of 12 to a maximum of 32 participants will be enrolled in Part 1, starting at the target dose (dose level 1 of 80 mg) and dose de-escalation, as needed. Dose-limiting toxicities (DLTs) and the tolerability of odronextamab will be assessed. All participants will only receive odronextamab in Part 1. The odronextamab dose in previously untreated FL participants will be determined after at least 12 DLT-evaluable participants have been treated and after the safety has been evaluated by the sponsor. In the event that the lower dose is selected, 8 additional participants will be enrolled in this dose level. The safety and efficacy of at least 20 participants treated at this dose level (including 12 patients from the BOIN evaluation) with adequate follow up will be evaluated to support the proposed dose prior to the initiation of Part 2.

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	Participants will receive 6 cycles of odronextamab monotherapy. Six weeks following the end of cycle 6 (W24 assessment), participants with complete response (CR) or partial response (PR) will continue to the maintenance therapy period with odronextamab monotherapy (12 doses given every 8 weeks [Q8W]). **Part 2:** Approximately 446 participants will be enrolled and will be randomly assigned in a 1:1 ratio to receive either (A) odronextamab followed by odronextamab maintenance or (B) rituximab in combination with chemotherapy followed by rituximab maintenance. Selection of chemotherapy will be according to the investigator's clinical judgement. Randomization will be stratified according to Follicular Lymphoma International Prognostic Index 1 (FLIPI 1) score (0 or 1 [low risk], 2 [intermediate risk], or 3 to 5 [high risk]); longest lesion diameter (≤6 vs. >6 cm); and age (< 65 vs. ≥ 65 years old). Participants will receive 6 cycles of either odronextamab monotherapy or rituximab with chemotherapy. At the end of cycle 6, participants assigned to receive odronextamab monotherapy with CR or PR will continue to receive odronextamab monotherapy with a dose of 320 mg Q8W for up to 12 doses until disease progression, loss to follow-up, or withdrawal of consent, whichever is earliest. For participants assigned to receive rituximab combined with chemotherapy, the treatment will be per standard practice, 6 cycles of induction chemotherapy, followed by up to 12 doses of rituximab monotherapy at Q8W intervals (participants with CR and PR only) or until disease progression, loss to follow-up, or withdrawal of consent, whichever is earliest.

Study Duration	The duration of the study varies for individual participants and includes:
	
	• A screening period of up to 28 days
	• A treatment period as outlined below:
	  o For participants on Part 1 (Safety Run-in): 6 cycles of odronextamab monotherapy and for participants in CR or PR, 12 doses of monotherapy as maintenance therapy
	  o For participants on Part 2 (Randomized Phase): randomized treatment consisting of 6 cycles of odronextamab monotherapy or rituximab with chemotherapy and, for participants in CR or PR, 12 doses of odronextamab or rituximab as maintenance therapy
	• Clinical Follow-Up: visit 90 days after the last dose or until the start of next non-protocol anti-lymphoma therapy This will be followed by visits every 12 weeks from day 90 after last dose until disease progression, withdrawal of consent, loss to follow-up, death, start of next anti-lymphoma treatment, or

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	end of study (EOS), whichever is earliest. This period only applies to participants who discontinue study treatment for reasons other than disease progression or withdrawal of consent. • Survival Follow-Up: survival status collected every 12 weeks will apply for participants who end the study, and it will continue until death, withdrawal of consent, loss to follow-up (ie, study participant can no longer be contacted or have the survival status verified by the investigator) or study termination by the sponsor, whichever is earliest. End of study (EOS) for a participant is defined as the time when a participant completes the last study visit and/or last study procedure, dies, withdraws consent, or is lost to follow-up (ie, the study participant can no longer be contacted by the investigator).
End of Study Definition	The definition for End of Study (Trial) is the date of the global last participant's last visit, date of withdrawal from the study, or loss to follow-up.
Population	
Sample Size:	In Part 1, 12 to 32 participants will be enrolled. In Part 2, an estimated 446 participants (approximately 223 participants in each treatment arm) will be enrolled.
Target Population:	Participants with the following criteria will be enrolled in this study: • Have diagnoses of $CD20^+$ FL grade 1-3a, stage II bulky or stage III / IV: Local histopathologic confirmation of the $CD20^+$ FL grade 1 to 3a, must be obtained before study enrollment. Biopsies must have been obtained within 18 months prior to study enrollment. In Part 1, a FLIPI score of 3 to 5 is required. • Need for treatment as indicated: Presence of ≥1 of the following: B symptoms, large tumor mass (characterized by lymphomas with a diameter >3 cm in 3 or more regions or by a lymphoma with a diameter >6 cm in 1 region), and presence of lymphoma-related complications. • Have measurable disease on cross-sectional imaging documented by diagnostic computed tomography [CT], or magnetic resonance imaging [MRI] (measurable disease is defined as at least 1 bidimensionally measurable nodal lesion of >1.5 cm or extranodal disease of >1 cm in the greatest transverse diameter (GTD) regardless of the short axis diameter). • Eastern Cooperative Oncology Group (ECOG) performance status of 0-2.

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	In addition, participants must have evidence of adequate hepatic, renal, and cardiac function.

Treatment(s)

Study Drug	Odronextamab
Dose/Route/Schedule:	Odronextamab will be administered by intravenous (IV) infusion at an initial dose of 0.7 mg (split as 0.2 mg on cycle 1 day 1 and 0.5 mg on cycle 1 day 2), an intermediate dose 1 of 4 mg (split as 2 mg on cycle 1 day 8 and 2 mg on cycle 1 day 9), followed by intermediate dose 2 of 20 mg (split as 10 mg on cycle 1 day 15 and 10 mg on cycle 1 day 16). From cycle 2 up to cycle 4, odronextamab will be administered IV on days 1, 8, and 15 at 80 mg dose (dose level 1 for Part 1). In cycle 5 odronextamab will be administered IV on day 8, and in cycle 6 it will be administered on day 1 and 15 at 160 mg. During the monotherapy maintenance treatment period, odronextamab will be administered IV each Q8W at 320 mg.
Comparator Drug	Rituximab
Dose/Route/Schedule:	Rituximab will be administered IV on day 1 of each cycle at a dose of 375 mg/m^2. When administered subcutaneously the dose will be 1,400 mg/ 23,400 units hyaluronidase human, given on day 1 of each cycle. All participants must receive at least 1 full dose of a rituximab product by IV infusion before receiving rituximab injection.
Chemotherapy	Cyclophosphamide
Route/Schedule:	Cyclophosphamide will be administered IV on day 1 of each cycle for 6 cycles at a dose of 750 mg/m^2.
Chemotherapy	Doxorubicin
Route/Schedule:	Doxorubicin will be administered IV on day 1 of each cycle for 6 cycles at a dose of 50 mg/m^2.
Chemotherapy	Vincristine
Route/Schedule:	Vincristine will be administered IV on day 1 of each cycle for 6 cycles at a dose of 1.4 mg/m^2.
Chemotherapy	Prednisone/prednisolone
Dose/Route/Schedule:	Prednisone/prednisolone will be administered orally (PO) on days 1-5 of each cycle for 6 cycles at a dose of 100 mg.
Chemotherapy	Bendamustine
Dose/Route/Schedule	Bendamustine will be administered IV on days 1-2 of each 28-day cycle for 6 cycles at a dose of 90 mg/m^2.

Endpoints

Primary:

Part 1

- The incidence of DLTs for odronextamab during the DLT observation period
- The incidence and severity of treatment-emergent adverse events (TEAEs) of odronextamab

Part 2

Complete Response at 30 months (CR30) at the week 120 assessment as assessed by independent central review according to the Lugano Classification (Cheson, 2014a)

Key Secondary:

Part 2

- Progression-free survival (PFS) defined as the time from randomization to the earliest date of disease progression according to the Lugano Classification or death from any cause as assessed by independent central review
- Event-free survival (EFS) defined as the time from randomization to the earliest date of disease progression according to the Lugano Classification, death from any cause, or the start of new therapy for lymphoma as assessed by independent central review
- CR30 at the week 120 assessment as assessed by local investigator according to the Lugano Classification (Cheson, 2014a)
- Overall mean change from baseline in physical function (EORTC-QLQ-C30)
- Overall Survival (OS) defined as the time from randomization to death from any cause

Secondary:

Part 1

- Odronextamab concentrations in serum
- Incidence and titer of anti-odronextamab antibodies (ADAs) and incidence of neutralizing antibodies (NAbs) to odronextamab over time
- Achieving objective response at end of induction and end of maintenance assessed by the investigator

Part 2

- Progression free survival (PFS) as assessed by local investigator
- Event free survival (EFS) as assessed by local investigator
- Achieving objective response assessed by local investigator and independent central review, defined as the percentage of participants whose best response is CR or PR

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	• Duration of response (DOR), assessed by independent central review and local investigator, defined as time from achieving response (CR/PR) to disease progression according to the Lugano Classification • Time to next anti-lymphoma treatment (TTNT) • Incidence and severity of TEAEs • Odronextamab concentrations in serum during the induction period and maintenance period • Incidence and titer of ADAs and incidence of NAbs to odronextamab over time • Overall mean changes in scores of PROs, as measured by the validated instruments EORTC-QLQ-C30, FACT-G GP5 question, FACT-LymS PGIS, PGIC, and EQ-5D-5L. • Change in score of the GP5 item in the participant population from first administration to end of treatment
Procedures and Assessments	For all participants, the disease will be assessed radiologically using CT or MRI and by ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET) imaging. Tumor response according to the Lugano Classification criteria will be performed by independent central radiology review. Bone marrow aspirate, bone marrow biopsy (BMA/BMx), and lymph node and/or tumor biopsy will be performed, and samples will be evaluated histologically and may be used for other exploratory studies, including for immunohistochemistry. Safety will be evaluated by the assessment of vital signs, physical examination, ECOG performance status, electrocardiogram (ECG), incidence of AEs, and reporting of concomitant medications. Laboratory evaluations will include complete blood counts with differential, blood chemistry values, serum immunoglobulin G (IgG), and serum pregnancy testing (if relevant). Blood samples for PK and ADA assessment will be collected in participants administered odronextamab. Peripheral blood samples will be collected to assess changes in biomarkers (e.g. serum levels of pro-inflammatory cytokines and changes in lymphocyte subsets and activation status). In addition, these samples will permit tumor or somatic genetic analyses for variations that impact the clinical course of underlying disease or modulate treatment side effects. Quality of life assessments will be performed electronically using the self-administered EORTC-QLQ-C30, FACT-G GP5 question, FACT- LymS, PGIC, PGIS, and EQ-5D-5L questionnaires.
Statistical Plan	**Part 1**
Justification of Sample Size	Twelve (12) to 32 participants may be enrolled. The actual sample size will depend on the number of DLT-evaluable participants. **Part 2** Assuming a CR30 rate of 53% in participants treated with rituximab combined with chemotherapy and a CR30 rate of 68% in participants treated with odronextamab, a sample size of 446 participants will yield

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	approximately 90% power to detect an improvement of 15% in CR30 rate with an overall 2-sided type I error of 0.05.
Efficacy Analyses	The Full Analysis Set (FAS) for Part 1 includes all participants who received any study drug. The efficacy analyses for Part 1 will be performed based on the FAS. The FAS for Part 2 includes all randomized participants. The efficacy analyses for Part 2 will be performed based on the FAS according to the treatment randomized, per intent-to-treat (ITT) principle. **Primary Efficacy Analysis** The primary endpoint of CR30 rate at the week 120 assessment per independent central review according to the Lugano Classification Response Criteria will be analyzed by the Cochran-Mantel–Haenszel (CMH) test using the following stratification factors at randomization: • Follicular Lymphoma International Prognostic Index (FLIPI) score (0 or 1 [low risk] vs. 2 [intermediate risk] vs. 3 to 5 [high risk]) • Longest lesion diameter (≤6 cm vs. >6 cm) An associated odds ratio and its 95% confidence interval (CI) will be estimated. A CR30 rate with the corresponding 95% exact CI will be calculated by the Clopper-Pearson method for each treatment arm. **Key Secondary Efficacy Analyses** PFS and EFS assessed by independent central review according to the Lugano Classification, and OS will be analyzed. The hazard ratio (HR) and its 95% CI will be estimated by a stratified Cox regression model with the same stratification factors used in analysis of CR30 rate. The median time and its 95% CI will be calculated using the Kaplan-Meier method for each treatment arm. CR30 rate at the week 120 assessment by local investigator, according to Lugano Classification, will be analyzed as described above for the primary efficacy analysis. Change from baseline of EORTC-QLQ-C30 physical functioning will be analyzed using the Mixed-Effect Model Repeated Measure (MMRM) model. **Secondary Efficacy Analyses** ORR at EOI and at end of maintenance assessed by independent central review and by local investigator review according to Lugano Classification will be analyzed using the CMH test. An associated odds ratio and 95% CI will be calculated. An ORR with the corresponding 95% exact CI will be calculated by the Clopper-Pearson method for each treatment arm. DOR, assessed by independent central review and by local investigator review; PFS and EFS assessed by local investigator review according to Lugano Classification; TTNT will be analyzed.

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	PRO summary statistics of absolute scores and change from baseline by visit will be reported for each scale/item of EORTC-QLQ-C30, FACT-LymS, FACT-G GP5, and EQ-5D-5L index and EQ VAS. Line charts depicting the mean and mean change from baseline will be provided. Summary statistics by visit for PGIS and PGIC will also be reported. **Control of Multiplicity** The multiplicity is controlled at 2-sided α 0.05 level. A hierarchical testing procedure will be used to adjust for multiple statistical testing of the primary and key secondary efficacy endpoints.
Safety Analyses	Demographic and baseline characteristics will be summarized descriptively. All AEs reported in this study will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). Summary of TEAEs, deaths, other SAEs, and TEAEs leading to permanent treatment discontinuation will be summarized by treatment group. Other safety parameters, including vital signs (temperature, pulse, blood pressure, pulse oximetry [on dosing days], and respiration rate), and laboratory tests will be summarized by baseline, and change from baseline to each scheduled assessment timepoint with descriptive statistics. Treatment duration and dose intensity will be summarized.
Interim Analysis	After the primary analysis of CR30, one formal interim efficacy analysis is planned for the key secondary endpoint of PFS, when approximately 130 PFS events (75% of total events) are observed. A formal interim efficacy analysis of EFS will also be performed at the time of the PFS interim efficacy analysis. The details are provided in Section 11.5.

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1. INTRODUCTION

Non-Hodgkin lymphomas (NHLs) comprise a heterogeneous group of malignancies that arise from lymphoid cells. Collectively, NHLs comprise the seventh most common malignancy and account for approximately 4.5% of all cancers occurring in the US. The American Cancer Society estimates that about 80,470 people will be diagnosed with NHL in 2022 and about 20,250 people will die from this cancer. In Europe, the estimated incidence of NHL in 2018 was 115,118 with a mortality of 48,096 (Global Cancer Observatory, 2020). The largest proportion of NHLs (>90%) are of B-lymphoid origin, and the remainder are Natural killer/ T-cell (T/NK)-lymphomas or are of indeterminate or mixed lineage (Teras, 2016). NHLs are commonly grouped into those that exhibit an initially indolent clinical course (indolent lymphomas such as follicular lymphoma (FL) and marginal zone lymphoma) and those that are typically aggressive (such as diffuse large B-cell lymphoma) at the time of initial presentation.

1.1. Follicular Lymphoma

Among the most common NHL subtypes are those of mature B-cells (B-NHL) (Swerdlow, 2017), and among these FL is the most prevalent. Follicular lymphoma (FL) is the most common indolent NHL in Western countries with an annual incidence of 3.4–5 per 100,000 in Europe and the U.S (Teras, 2016).

The initial treatment of advanced FL provides meaningful responses in a large proportion of patients, but high-risk groups have been identified in which the response duration is brief. In a retrospective evaluation of patients with previously untreated advanced FL, patients with high-risk clinical and molecular features had a 5-year failure-free survival of 25.0 to 38.3% (Pastore, 2015). In patients prospectively evaluated in the National LymphoCare Study who received front-line chemo-immunotherapy for FL, 20% of patients experienced progressive disease within 2 years of diagnosis, and for these patients the 5-year overall survival (OS) was 50% (Casulo, 2015); other retrospective evaluations have confirmed this finding (Maurer, 2016). In rituximab-based non-chemotherapy doublet trials, progression of disease (POD) within 24 months was associated with a 5-year survival of 74% compared to 90% for patients who did not have POD within 2 years (Lansigan, 2019).

Despite the effectiveness of chemo-immunotherapy in the first-line treatment setting, relapses occur in almost all patients; response durations are progressively shorter with successive lines of therapy, and disease relapse is the cause of death in most patients (Sorigue, 2016). In addition, transformation to a more clinically aggressive large cell lymphoma occurs at a rate of approximately 2 to 3% per year in the era of chemo-immunotherapy treatment (e.g., rituximab with chemotherapy) (Wagner-Johnston, 2015).

1.2. Odronextamab: An Anti-CD20 x Anti-CD3 Bispecific Antibody

REGN1979 (odronextamab) is a human IgG4-based bispecific antibody that binds to CD20, a B-cell surface antigen present on normal and malignant B-cells, and to CD3, a T-cell antigen associated with the T-cell receptor complex. Odronextamab is designed to bridge CD20-expressing cells with cytotoxic T-cells by binding the CD3 subunit of the T-cell receptor, resulting in CD20-directed polyclonal T-cell killing. The T-cell activation is dependent on the presence of the target, in this case CD20. The cytotoxic T-cell response seen with the anti-CD20 x anti-CD3

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bispecific antibody is thus independent of the typical requirements for specific T-cell receptor recognition of a target cell. This novel mechanism of action is distinct from that of anti-CD20 antibodies and as such may also provide a therapeutic benefit in patients who have relapsed following anti-CD20 monoclonal antibody therapy.

Targeting the CD3 subunit of the T-cell receptor (TCR) in conjunction with a tumor-associated antigen (TAA) has been shown to activate cytotoxic T cells to kill antigen-bearing tumor cells both in vitro and in vivo (Cochlovius, 2000) (Laszlo, 2014) (Friedrich, 2012). Several clinical studies have validated the use of CD3 x TAA bispecific antibodies in general and targeted T-cell killing of hematologic malignancies (Maher, 2013). CD20 is expressed on immature and mature B cells, as well as memory B cells from blood and lymphoid organs, but is not expressed on precursor B cells in the bone marrow or on antibody-producing plasma cells. CD20 is also expressed in various types of malignant B-cells and is a clinically validated target for immunotherapy. Mosunetuzumab, another bispecific T-cell engager (BiTE) monoclonal antibody directed at both CD20 on FL cells and CD3 on cytotoxic T cells, showed durable complete responses (CRs) in patients with relapsed or refractory B-cell lymphoma in a Phase 1 dose-escalation study and has been approved by the European Medicines Agency for adults with relapsed or refractory FL who have received at least two prior systemic therapies.

Dosing, safety, and preliminary efficacy of odronextamab have been explored in study R1979-HM-1333 (Study 1333), a phase 1 first-in-human trial of odronextamab monotherapy in patients with relapsed or treatment-refractory B-NHL or chronic lymphocytic leukemia, and in the study R1979-ONC-1625 (Study 1625), a phase 2, open-label study in patients with relapsed or refractory B-NHL.

As of the safety data cut-off date of 18 Sep 2022, a total of 539 participants have been treated with odronextamab monotherapy treatment, with estimated exposure of 9842 patient weeks. Treatment-related treatment-emergent adverse events (TEAEs, all grades) reported in ≥20% of patients were cytokine release syndrome (CRS) (55.8%), pyrexia (36.2%) neutropenia/neutrophil count decreased (25.6%) and infusion related reaction (IRR) (25.8%). Infections were reported in 26.9% of patients and potential Immune effector cell-associated neurotoxicity syndrome (ICANS) events were reported in 7.8% of patients.

A total of 322 of the 539 patients (59.7%) treated with odronextamab monotherapy experienced grade ≥3 treatment-related TEAEs (assessed by the investigators). The most commonly reported (≥ 10%) grade ≥3 treatment-related TEAEs were neutropenia/neutrophil count decreased (20.8%) and anemia (10.0%). Grade 3 or higher infections were reported in 12.6 % of patients and Grade 3 or higher potential ICANS events reported in 2% of patients. Adverse events reported to date were generally consistent with the mechanism of action of odronextamab or the underlying malignancy.

Step-up dosing regimen was revised to decrease incidence and severity of CRS, as of the 18 Sep 2022, of the 166 patients treated with the revised step-up regimen of 07/4/20 mg, 86 (51.9%) patients experienced CRS, highest grade of CRS observed was grade 1 in 62 (37.3%) patients, grade 2 in 21 (12.7%) patients and grade 3 in 3 (1.8%) of patients.

The revised step-up dosing regimen was successful in reducing the incidence and severity of CRS events. Incidence of any grade CRS events decreased from 183/300 (61%) patients with the 1/20 regimen to 86/166 (51.8 %) patients with the revised regimen and grade 3 or higher CRS events

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decreased from 8.7% with the 1/20 regimen to 1.8% with the revised regimen. In addition, the overall incidence of grade 2 or higher CRS events decreased from 28.3% with the 1/20 regimen to 14.5% with the revised regimen. No patient experienced grade ≥2 CRS after the first full dose.

Study 1333 has demonstrated promising efficacy for odronextamab monotherapy in B-NHL patients who had a median of 3 prior lines of therapy. As of 16 Mar 2022, the overall response rate (ORR) in 40 FL patients was 77.5% (95% CI: 61.5% to 89.2%) as assessed by the investigator. The median estimated DOR was 15.8 months (95% CI: 6.4, not evaluable [NE]), and median PFS per investigator assessment at the time of data cutoff was 12.8 months (95% CI: 6.4, NE).

In Study 1625, as of the cutoff date of 20 Apr 2022, odronextamab has demonstrated clinically meaningful efficacy in patients with FL grade 1-3a who were heavily pretreated patients with a median of 3 prior lines of systemic therapies, including ORR of 81% and CR of 75% as assessed by independent central review. The Kaplan-Meier (KM)-estimated median duration of response (DOR; CR/PR) is 18.2 months (14.8, NE), and median duration of CR is 18.2 months (14.8, NE) based on median duration of follow-up of 17.3 months (14.4, 19.4). The median PFS and median OS times are KM estimated to be 20.2 months (14.8, NE) and not reached (NR) (23.0, NE), respectively.

For additional information on the non-clinical and clinical studies conducted with odronextamab, see the Investigator's Brochure (IB).

This study will include participants with untreated FL. In part 1 (Safety Run-in) the safety of odronextamab will be evaluated as the primary objective, and in part 2 (Randomized Phase) the anti-tumor activity of odronextamab versus standard-of-care immune-chemotherapies, selected at the treating investigator's discretion of the National Comprehensive Cancer Network (NCCN) recommended therapies for this indication, which are cyclophosphamide, doxorubicin, vincristine, and prednisone (collectively CHOP); cyclophosphamide, vincristine, and prednisone/prednisolone (collectively CVP); and bendamustine, all with rituximab.

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2. STUDY OBJECTIVES

Table 1: Study Objectives – Part 1 (Safety Run-in)

Objectives	Endpoints
Primary Objective	
Assess the safety, tolerability, and dose-limiting toxicities (DLTs) of odronextamab in participants with previously untreated FL	The incidence of DLTs for odronextamab during the DLT observation period The incidence and severity of treatment-emergent adverse events (TEAEs) of odronextamab
Secondary Objectives	
To characterize the pharmacokinetics (PK) of odronextamab	Odronextamab concentrations in serum
To assess the immunogenicity of odronextamab	Incidence and titer of anti-odronextamab antibodies (ADAs) and incidence of neutralizing antibodies (NAbs) to odronextamab over time
To evaluate the preliminary anti-tumor activity of odronextamab	Achieving objective response as assessed by the investigator by: • End of induction (cycle 6) and • End of maintenance
Exploratory Objectives	
To assess the association between clinical safety of odronextamab with biomarkers of systemic immune activation (serum cytokine levels, immune cell counts, and phenotypes)	• Changes in absolute numbers of peripheral T- and B-cells, measured by multiparameter flow cytometry • Changes in patterns of serum cytokine elevation
To assess other pharmacodynamic, predictive, or prognostic biomarkers associated with odronextamab that are potentially related to safety	Associations between odronextamab concentrations, biomarkers, and TEAEs

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Table 2: Study Objectives – Part 2 (Randomized Phase)

Objective(s)	Endpoint
Primary Objective	
To compare the efficacy of odronextamab versus investigator's choice chemotherapy in participants with previously untreated FL as measured by CR30 per independent central review	Complete Response at 30 months (CR30) at the week 120 assessment as assessed by independent central review according to the Lugano Classification (Cheson, 2014a)
Key Secondary Objectives	
To compare the efficacy per independent central review between odronextamab monotherapy and investigator's choice chemotherapy as measured by: • PFS • Event-free survival (EFS)	• PFS defined as the time from randomization to the earliest date of disease progression according to the Lugano Classification or death from any cause as assessed by independent central review • EFS defined as the time from randomization to the earliest date of disease progression according to the Lugano Classification, death from any cause, or the start of new therapy for lymphoma as assessed by independent central review
To compare the efficacy of odronextamab monotherapy versus investigator's choice chemotherapy as measured by CR30 per investigator	CR30 at the week 120 assessment as assessed by local investigator according to the Lugano Classification
To evaluate the treatment effects on patient-reported physical function between odronextamab monotherapy and investigator's choice chemotherapy utilizing EORTC-QLQ-C30	Overall mean change from baseline in physical function (EORTC-QLQ-C30)
To compare the efficacy of odronextamab monotherapy versus investigator's choice chemotherapy as measured by OS	OS defined as the time from randomization to death from any cause
Secondary Objectives	
To assess additional measures of efficacy of odronextamab compared to investigator's choice chemotherapy	• PFS as assessed by local investigator • EFS as assessed by local investigator • Achieving objective response assessed by local investigator and independent central review, defined as the percentage of participants whose best response is CR or partial response (PR) according to the Lugano Classification

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Objective(s)	Endpoint
	• DOR, assessed by independent central review and local investigator, defined as time from achieving response (CR/PR) to disease progression according to the Lugano Classification • Time to next anti-lymphoma treatment (TTNT)
To evaluate safety and tolerability of odronextamab compared to investigator's choice chemotherapy	Incidence and severity of TEAEs
To evaluate the PK of odronextamab	Odronextamab concentrations in serum during the induction period and maintenance period
To assess the immunogenicity of odronextamab	Incidence and titer of ADAs and incidence of NAbs to odronextamab over time
To evaluate the effect of odronextamab compared to investigator's choice chemotherapy impact on patient-reported outcomes (PROs), including health related quality of life (HRQoL), as measured by the validated instruments European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30), Functional Assessment of Cancer Therapy – Lymphoma, lymphoma subscale (FACT-LymS), Patient Global Impression of Severity (PGIS), Patient Global Impression of Change (PGIC), and EuroQoL-5 Dimension-5 Level Scale (EQ-5D-5L)	Overall mean changes in scores of PROs, as measured by the validated instruments EORTC-QLQ-C30, FACT-LymS, PGIS, PGIC, and EQ-5D-5L
To evaluate the patient-reported overall impact of treatment toxicity using the GP5 item of the validated Functional Assessment of Cancer - General (FACT-G) questionnaire	Change in score of the GP5 item in the participant population from first administration to end of treatment
Exploratory Objectives	
To evaluate the association between circulating tumor DNA (ctDNA) and clinical response	Changes in ctDNA at specified timepoints during treatment and follow-up periods by next generation sequencing
To assess the association between clinical safety of odronextamab with biomarkers of systemic immune activation (serum cytokine levels, immune cell counts, and phenotypes)	• Changes in absolute numbers of peripheral T- and B-cells, measured by multiparameter flow cytometry • Changes in patterns of serum cytokine elevation

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Objective(s)	Endpoint
To evaluate the association between disease response and the count and phenotype of tumor-infiltrating T cells and tumor B-cell target antigen expression, both at baseline and at progression	Association of response with lymph node T-cell density and expression of immune markers. These may include CD28, programmed death receptor-1 (PD-1), PD-L1, and Lag3 and with B-cell markers (CD20, CD22). These will be measured by multiplex immunohistochemistry (IHC) and/or next generation sequencing.
To assess other pharmacodynamic, predictive, or prognostic biomarkers dependent on odronextamab that are potentially related to anti-tumor activity and safety	Associations between odronextamab concentrations, biomarkers, and TEAEs

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3. HYPOTHESIS AND RATIONALE

3.1. Hypothesis

Odronextamab monotherapy is associated with superior anti-tumor efficacy as measured by CR30 compared to investigator's choice of immuno-chemotherapy (see Section 3.2.1.2 for details) for participants with previously untreated FL.

3.2. Rationale

3.2.1. Rationale for Study Design

This is a phase 3, open-label, randomized study comparing the efficacy and safety of odronextamab monotherapy to standard of care immune-chemotherapy selected by the investigator in previously untreated participants with FL. Because of the different administration schedules for each treatment arm, it is not feasible to conduct the study in a blinded manner; therefore, it will be conducted as open label.

The safety run-in phase (part 1) will examine the safety and tolerability of odronextamab in order to define the dose of odronextamab for the randomized phase (part 2) of the study.

The target population is adult patients with previously untreated FL. Study 1333 and Study 1625 have demonstrated promising efficacy for odronextamab monotherapy in B-NHL patients who had a median of 3 prior lines of therapy as described in Section 1.2. The current study compares odronextamab monotherapy with investigator's choice chemotherapy, selected by the investigator (See Section 3.2.1.2 for details), in previously untreated FL participants. The primary endpoint is CR30, which is a validated surrogate endpoint for PFS in the setting of previously untreated FL based on a large, individual patient data metanalysis of 3,837 patients from 13 randomized trials (Shi, 2017). Given the observed, durable benefit of odronextamab in highly refractory indolent lymphoma, there is a potential to further improve outcomes in earlier lines of therapy.

3.2.1.1. Rationale for Dose Selection and Selection of Control

Odronextamab monotherapy has demonstrated preliminary efficacy in relapsed/recurrent (R/R) FL that is refractory to prior CD20 antibody therapy. It is hypothesized that odronextamab would improve the efficacy as demonstrated by CR30 and therefore PFS in the front-line setting as well, compared to rituximab in combination with chemotherapy.

The odronextamab regimen in this study consists of step-up doses in cycle 1 (21 days total), weekly doses on days 1, 8, and 15 in cycles 2-4, biweekly treatment doses in cycles 5-6 (day 8 in cycle 5 and days 1 and 15 in cycle 6), and every 8 weeks (Q8W) maintenance doses thereafter.

The step-up doses in cycle 1 (weeks 1-3) consist of 0.7 mg at week 1 (0.2 mg/ 0.5 mg split on day 1 and day 2), 4 mg at week 2 (2 mg/ 2 mg split on day 8 and day 9), and 20 mg at week 3 (10 mg/ 10 mg split on day 15 and day 16). The step-up doses along with premedications have been previously tested in more than 100 patients with R/R FL, R/R diffuse large B-cell lymphoma (DLBCL), or other B-NHL in Study 1333 and Study 1625 and are generally well tolerated and associated with low incidences of grade 3 CRS (see Section 1.2). For evaluation of the safety profile of the step-up doses in the previously untreated patients with FL, a safety run-in phase will be implemented prior to the randomized portion of the study.

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The treatment doses in cycles 2-4 and cycles 5-6 consists of 80 mg on days 1, 8, and 15 and 160 mg on day 8 (cycle 5) and days 1 and 15 in cycle 6, respectively (dose level 1 for Part 1). The regimen has been studied in patients with grade 1-3a FL in Study 1625 and showed promising efficacy in this patient population. The reported ORR was 81%, and the CR rate was 75% (n=85) based on a prespecified interim analysis (20 Apr 2022 data cut). Therefore, the above-mentioned treatment regimen of odronextamab is selected for untreated patients with FL.

The maintenance treatment consists of 320 mg Q8W odronextamab monotherapy for up to 12 doses or until disease progression, whichever is earlier. Both efficacy and safety aspects were considered in the selection of the maintenance dosing regimen. From an efficacy perspective, deep and durable responses were found in patients with R/R FL at odronextamab doses ≥ 5 mg QW in Study 1333. As odronextamab exhibits non-linear PK properties, a developed population PK model was used to predict steady state trough and average concentrations of a 320 mg Q8W dosing schedule for evaluation of odronextamab exposures with the Q8W regimen. Based on simulations, the predicted mean (standard deviation [SD]) steady state trough concentration is 5.35 (5.23) mg/mL and the average concentration over the 8-week dosing interval is 19.3 (8.30) mg/L. The predicted mean (SD) trough concentration value (5.35 (5.23) is similar to the observed mean (SD) trough concentration at week 12 with 27 mg QW dose (5.75 (3.26)). The predicted mean (SD) average concentration (19.3 (8.30) is higher than the observed mean (SD) trough concentration at week 12 with 40 mg QW dose (9.23 (5.34)) in Study 1333 (odronextamab IB V6). Since durable and complete responses have been observed in the setting of refractory indolent lymphoma with doses as low as 5 mg QW and clinical response was maintained when the 160 mg Q2W dose was changed to 160 mg every 4 weeks (Q4W) in patients who had CR for 9 months in Study 1625, investigating an extended period of odronextamab monotherapy of 320 mg Q8W, after completion of 80 mg QW/160 mg Q2W dosing during the induction treatment, is supported. From a safety perspective, the re-emergence of cytokine release is highly unlikely to be observed at the predicted odronextamab concentrations during maintenance (after cycle 6), based on experience obtained from Study 1333. The proposed maintenance period for up to 12 doses of Q8W is comparable to the schedule of rituximab maintenance therapy, which is the standard of care.

3.2.1.2. Selection of Investigator's Choice

The current standard of care for previously untreated indolent lymphoma patients is 6 cycles of rituximab-based induction chemotherapy followed by an extended period of rituximab monotherapy dosing for 12 cycles at Q8W intervals, as referenced in NCCN and European Society for Medical Oncology (ESMO) guidelines. Rituximab in combination with CHOP (R-CHOP) or CVP (R-CVP) and bendamustine (BR) are all suggested first line regimens in NCCN guidelines and ESMO guidelines. The RELEVANCE study, which compared lenalidomide plus rituximab to rituximab-chemotherapy in untreated patients with FL, used the same 3 control arms (Morschhauser, 2018).

3.2.1.3. Rationale for Biomarker Sample Collection

Circulating tumor DNA (ctDNA) has been shown to be useful as a marker of measurable residual disease in DLBCL (Herrera, 2022) and also in FL (Kurtz, 2018).

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The change in ctDNA quantity on treatment associates with outcome (e.g. OS and DOR) and may be used as a marker of response. In addition, the variants (mutations, gene fusions, etc.) detected in the ctDNA may be used to classify patients into molecular subtypes (such as double hit and cell of origin) and to determine associations with treatment resistance.

To further investigate potential risks of infections in patients treated with odronextamab and to determine how the risks compare to those observed with the current standard of care, baseline and later-timepoint (6 months, 1 year, and 2 years on treatment) peripheral blood will be collected. T- and B-cell counts will be determined along with T-cell phenotype (e.g. activation, proliferation, exhaustion). Immunoglobulin G (IgG) levels will be determined at baseline and on treatment as well. In addition, as both CD20-directed monoclonal antibodies (such as rituximab) and odronextamab deplete B cells (as observed in Study 1333 and Study 1625 (Anolik, 2007), recovery of immune-cell count and phenotype will be determined at 24 weeks, 1 year, and 2 years after cessation of treatment.

Cytokine release syndrome (CRS) with odronextamab treatment was one of the risks observed in patients treated in Study 1625 (third and later lines of treatment). Increases in cytokines (such as interleukin 6 and interferon gamma) have been measured in these patients with CRS. The pattern of release of these cytokines may allow for distinguishing between CRS and other types of immune-mediated adverse events (e.g. infections and sepsis) (Fajgenbaum, 2020).

Since no data is available on odronextamab in a first line setting in FL, additional safety samples (cytokine and peripheral blood samples) will be collected in part 1 (safety run-in). The targets of odronextamab (CD20 and CD3) may be expressed differently in first line patients compared to third line patients.

3.2.2. Other Drugs Used in R1979-HM-2298 and the Latest Scientific Findings for Reference Safety Information

In this study, tocilizumab, rituximab, bendamustine, cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone are considered as drugs used in the clinical trial (DUICT) per the updated Good Clinical Practice-Japan (J-GCP) guidance. The summary of product characteristics (SmPC) will be used as the latest scientific findings for the reference to the safety evaluation.

3.2.3. Risk-Benefit

Odronextamab is an effective bispecific antibody for the treatment of B-cell malignancies, as described in Section 1.2. As described in Section 3.2, odronextamab monotherapy has shown clinical benefit in patients with relapsed/refractory FL. In this study, odronextamab monotherapy will be administered in first line FL in the hopes of improving patient outcomes while avoiding the toxic effects of chemotherapy.

The important risks of administering odronextamab and the mitigation strategies are presented in Table 3. Additional information and a risk-benefit statement with respect to the overall development program is provided in the odronextamab IB.

Table 3: Important Risks of Odronextamab and Mitigation Strategies

Risks of Clinical Significance	Rationale for Risk	Mitigation Strategy
CRS/ IRRs/ Systemic hypersensitivity reactions	There is significant overlap in the clinical presentation of CRS, IRR, and systemic hypersensitivity. The symptomatology associated with these entities is consistent with an underlying mechanism of exaggerated immune response and release of inflammatory cytokines. The T-cell engaging immunotherapy mechanism of action, such as odronextamab, is non-physiologic T-cell activation with the occurrence of cytokine release. Clinical effects of CRS can range from mild symptoms such as fever to a severe inflammatory syndrome, which may be life-threatening or lead to death. IRR/CRS has been observed with odronextamab monotherapy (see Odronextamab [REGN1979] IB).	Participants at high risk of hypersensitivity reactions are excluded (Section 7.2.2 Exclusion Criterion 27). Medications and equipment to manage medical emergencies must be available for immediate use before initiation of infusion. Administration of initial odronextamab infusions as split doses (Section 8.1.1), step-up doses. Use of dexamethasone, antihistamines, and antipyretics (Section 8.2.1) during cycles 1 and 2. Post medication with dexamethasone during cycles 1 and 2. Close monitoring following administration of initial doses (step-up doses) (Section 8.1.1). Guidelines for the grading and management of CRS are provided in Section 8.4.2, Table 16, Table 17, and Table 18.
Central nervous system (CNS) adverse events (ICANS)[1].	CNS symptoms such as confusion, delirium, and aphasia have been observed with T-cell engaging therapy and as part of CRS. These symptoms are now considered to be a separate syndrome (immune-effector cell-associated neurotoxicity syndrome [ICANS]). Cytokines may be implicated in the pathophysiology (Lee, 2019). Potential ICANS events have been observed with odronextamab monotherapy (please	Participants with CNS pathology are excluded (Section 7.2.2 Exclusion Criteria 11). Guidance on management including study drug administration is included (Section 8.4.3).

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Risks of Clinical Significance	Rationale for Risk	Mitigation Strategy
	refer to odronextamab [REGN1979] IB for details).	
Infections Including Hepatitis B [HBV] Reactivation)	Based on the mechanism of action, treatment with odronextamab may result in pronounced B-cell depletion and hypogammaglobulinemia. This in turn can result in increased risk of infections, including opportunistic infections and viral infections, including reactivation of hepatitis B virus. Infections have been observed with odronextamab monotherapy (please refer to odronextamab [REGN1979] IB).	Participants with known active infections are excluded (Section 7.2.2). Infection prophylaxis is recommended (Section 8.4.5). Protocol-defined assessments of immunoglobulin levels (Section 8.4.5).
Tumor Lysis Syndrome (TLS)	TLS is an oncologic emergency triggered by the rapid release of intracellular material from lysing malignant cells. TLS has been reported in virtually every cancer type. The highest risk of TLS is seen in large-volume, highly proliferative malignancies such as B-cell acute lymphoblastic leukemia (ALL) and Burkitt's lymphoma, whereas solid tumors and slow-growing hematologic malignancies carry lower risks (Wilson, 2014). TLS has been observed with odronextamab monotherapy (Odronextamab [REGN1979] IB).	Participants with hypersensitivity to both allopurinol and rasburicase are excluded (Section 7.2.2 Criterion 27). Guidance on prophylaxis, risk stratification, monitoring, and management of TLS are included (Section 8.4.4). Guidance on odronextamab dosing including interruption and re-challenge is included (Section 8.3.1).

[1]This is considered a potential risk in the IB.

3.2.3.1. Risk Benefit for Active Comparator

Rituximab with CHOP/CVP/bendamustine serves as the active comparator for this study and are all suggested first line regimens in NCCN guidelines and ESMO guidelines. See Section 3.2.1.2 for information on the rationale for use of these as the comparator.

3.2.4. Overall Benefit-Risk Conclusion

Taking into account the clinical activity with odronextamab monotherapy, measures implemented in the protocol to minimize important risks to participants, and the potential for therapeutic benefit, the evaluation of odronextamab in participants with previously untreated FL is supported.

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4. ENDPOINTS

Refer to Table 1 and Table 2.

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5. STUDY VARIABLES

5.1. Demographic and Baseline Characteristics

Baseline characteristics will include standard demography (e.g., age, race, and gender among others), disease characteristics, relevant medical and oncologic history, and treatment history.

5.2. Efficacy Variables

Efficacy variables include but are not limited to the following:

- CR30
- PFS
- EFS
- Best overall response
- DOR
- OS

Response will be measured by the Lugano Classification (Cheson, 2014a).

The efficacy variables will be assessed by the following procedures: computed tomography (CT), magnetic resonance imaging (MRI), ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET), bone marrow aspirate/biopsy (BMA/BMx), and Physical examination, including assessment for B symptoms as described in Section 9.2.2.

5.2.1. Patient-Reported Outcomes

The following assessments (described in Section 9.2.2.4) will be performed:

- Patient-reported general health status/QoL, symptoms, and functioning (per European Organization for Research and Treatment of Cancer Quality of Life Questionnaire [EORTC QLQ]-C30)
- Functional Assessment of Cancer Therapy – Lymphoma, lymphoma subscale (FACT-LymS)
- EuroQoL-5 Dimension-5 Level Scale [EQ-5D-5L]
- Global anchors of patient-reported outcomes per PGIS (Patient Global Impression of Severity) and PGIC (Patient Global Impression of Change)
- Single item GP5 from the FACT-G questionnaire to assess the overall impact to the participant of treatment toxicity

5.3. Safety Variables

The safety variables (described in Section 9.2.3) include:

- Treatment-emergent adverse events (TEAEs)
- SAEs

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- AESIs
- Vital signs
- Electrocardiogram (ECG)
- Physical examination
- Laboratory tests including immune safety assessments
- B symptoms assessment

5.4. Pharmacokinetic Variables

The PK variables are the concentration of odronextamab and time. The PK sampling timepoints are specified in (Table 27).

5.5. Immunogenicity Variables

The immunogenicity variables are ADA status, titer, neutralizing antibody (NAb) status, and timepoint/visit. Samples in this study will be collected at the clinic visits specified in Section 9.1.

5.6. Pharmacodynamic and Other Biomarker Variables

Pharmacodynamic and other biomarker variables include:

- Changes in absolute peripheral T and B cells and changes in patterns of serum cytokine elevation
- Lymph node T-cell density at baseline and at relapse of immune markers such as CD28, PD-1, PD-L1, and Lag3 along with B-cell markers (CD20, CD22)
- Longitudinal ctDNA measurements to assess measurable residual disease (MRD)
- DNA for pharmacogenomic studies/ analyses (optional)

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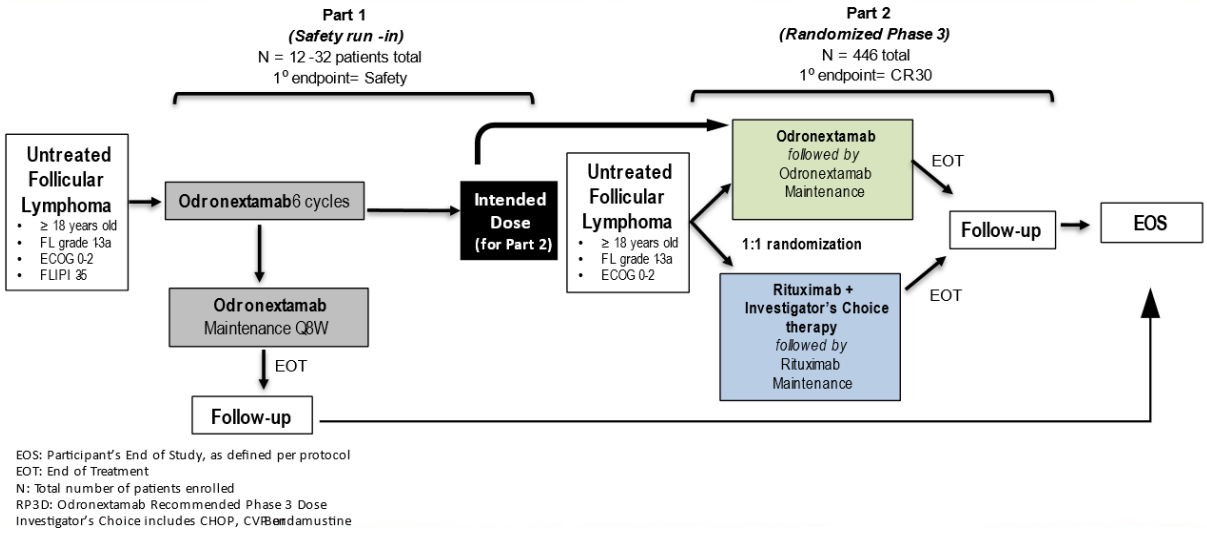
6. STUDY DESIGN

6.1. Study Description and Duration

This is an open-label, multicenter, randomized, phase 3 study to compare the efficacy and safety of odronextamab to investigator's choice of chemotherapy (Rituximab-CHOP, Rituximab-CVP, or Rituximab-Bendamustine) for treatment of participants with previously untreated FL. In Part 1 (safety run-in), the intended dose of odronextamab monotherapy to carry forward to Part 2 (randomized phase) will be tested. The efficacy and safety of the recommended dose of odronextamab will be evaluated in Part 2 versus investigator's choice of chemotherapy. All participants will receive 6 cycles of induction. At the end of cycle 6 induction, participants with CR or PR will continue to the maintenance therapy period with monotherapy treatment with either odronextamab or rituximab, depending on the study arm. Participants who relapse/progress during treatment or are in stable disease (SD) at the end of induction will be withdrawn from the treatment and continue to safety and survival follow-ups. Figure 1 illustrates the study design.

Figure 1: Study Flow Diagram



6.1.1. Study Periods

The study includes:

- A screening period of up to 28 days
- A treatment period as outlined below:
  - For participants on Part 1 (Safety Run-in): 6 cycles of odronextamab and, for participants in CR or PR at the end of induction, 12 doses of odronextamab as maintenance therapy.
  - For participants on Part 2 (Randomized Phase): randomized treatment consisting of 6 cycles of odronextamab monotherapy (induction) versus investigator's choice chemotherapy and, for participants in CR or PR at the end of induction, 12 doses of odronextamab or rituximab monotherapy as maintenance therapy.

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- Clinical Follow-Up visit 1: a visit at 90 days (±7 days) after the last dose or until the start of next non-protocol anti-lymphoma therapy. This period only applies to participants who discontinue induction or maintenance study treatment.
- Clinical Follow-Up Q12W: tumor assessment visits continue as planned with visits every 12 weeks (±7 days) until disease progression, withdrawal of consent, loss to follow-up, death, start of next anti-lymphoma treatment, or end of study, whichever is earliest. This period only applies to participants who discontinue study treatment for reasons other than disease progression or withdrawal of consent.
- Survival Follow-Up: survival status collected every 12 weeks will apply for participants who end the study, and it will continue until death, withdrawal of consent, loss to follow-up (i.e., study participant can no longer be contacted or have survival status verified by the investigator) or study termination by the sponsor, whichever is earlier.

End of study (EOS) for a participant is defined as the time when a participant completes the last study visit and/or last study procedure, dies, withdraws consent, or is lost to follow-up (i.e., the study participant can no longer be contacted by the investigator).

6.1.1.1. Screening Period

The screening period of up to 28 days duration begins with the signing of the informed consent form (ICF) and ends when the participant is confirmed to be eligible and has been assigned to the appropriate treatment arm or when the participant is considered ineligible (screen failure).

The screening assessments are detailed in Section 9.1. Participants may choose to participate in the optional genomics analysis by signing the related ICF, which is separate from the main ICF. CT-scan, PET-CT scan, and/or MRI that has been performed within the past 28 days (± 7 days) prior to first study treatment dose may be used, if done as required per protocol.

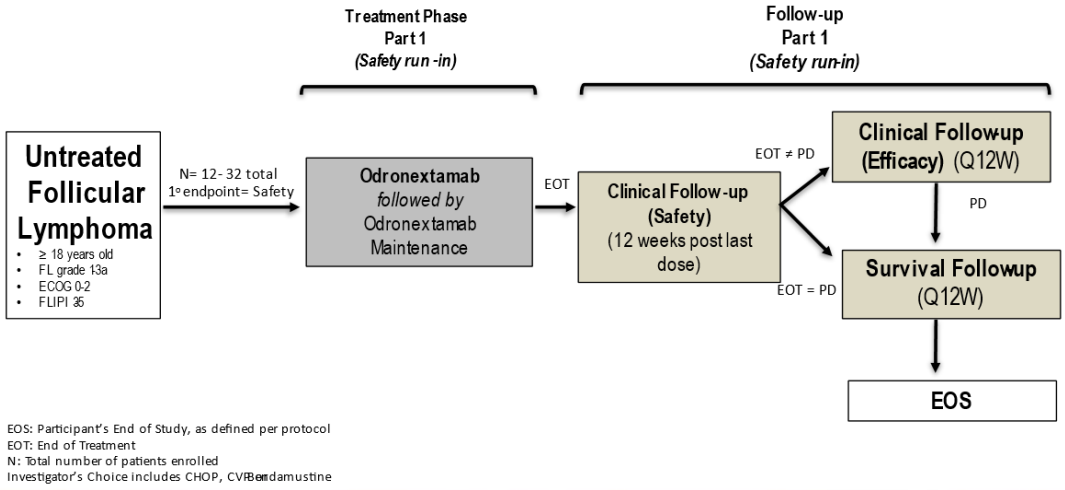
Rescreening is allowed. A new ICF must be signed before the re-screen. Some procedures may not need to be repeated if they were previously completed within 28 days (± 7 days) prior to first dose (or within 28 days (± 7 days) prior to first dose for CT-scan, PET-CT scan, and/or MRI).

6.1.1.2. Part 1: Safety Run-in

Participants with high-risk FL (Follicular Lymphoma International Prognostic Index 1 [FLIPI 1] score of 3-5) will be enrolled in the safety lead-in part.

A minimum of 6 participants will be enrolled at Dose Level 1 (DL1) with dose de-escalation (if needed) as per Table 4 and Section 6.1.2. Dose-limiting toxicities (DLTs) and the tolerability of odronextamab will be assessed (see Section 6.1.3). If the lower dose is selected, the efficacy and the safety of this dose will be assessed in at least 20 participants prior to selecting it for randomization in Part 2.

Figure 2: Participant Flow Diagram (Part 1, Safety Run-In)



6.1.1.3. Part 2: Randomized Phase

Approximately 446 participants will be enrolled and will be randomly assigned in a 1:1 ratio to receive either (A) odronextamab for induction, followed by odronextamab maintenance, or (B) investigator's choice of immuno-chemotherapy, followed by rituximab maintenance.

Selection of therapy (CHOP, CVP, or bendamustine) will be according to the investigator's clinical judgement.

Randomization will be stratified according to Follicular Lymphoma International Prognostic Index 1 (FLIPI 1) score (0 or 1 [low risk], 2 [intermediate risk], or 3 to 5 [high risk]), longest lesion diameter (≤ 6 vs. > 6cm), and age (< 65 vs. ≥ 65 years old).

For participants assigned to receive odronextamab, odronextamab will be given as monotherapy for 6 cycles at the dose selected during Part 1 (see Table 4). At the end of cycle 6, based on week 24 scan assessments, participants with CR or PR will continue treatment with odronextamab monotherapy at a dose of 320 mg Q8W for up to 12 doses or until disease progression, loss to follow-up, or withdrawal of consent, whichever is earlier. For participants assigned to receive rituximab combined with chemotherapy, the treatment will be per standard practice, 6 cycles of induction chemotherapy, followed by up to 12 doses of rituximab monotherapy at Q8W intervals (participants with CR and PR only), or until disease progression, loss to follow-up, or withdrawal of consent, whichever is earlier. Figure 3 illustrates participant flow in Part 2.

Study treatment is to begin within 5 days of randomization, unless approved by the medical monitor.

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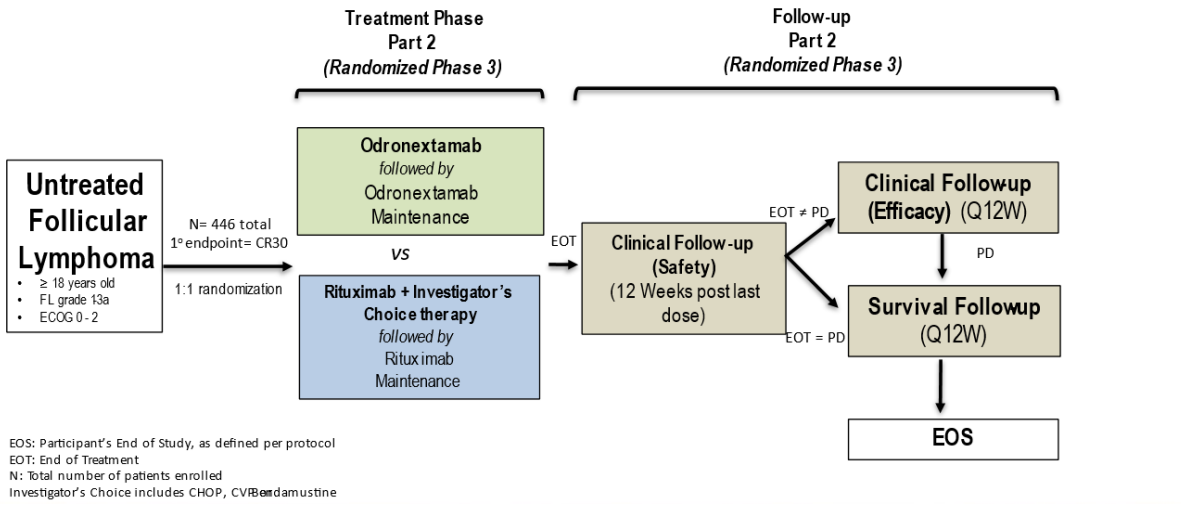
Figure 3: Participant Flow Diagram (Part 2, Randomized Phase)



The schedule for administration of odronextamab or rituximab combined with a chemotherapy regimen is described in Section 8.1.1 and Section 8.1.3.

6.1.1.4. Post-Treatment Follow-Up

The first clinical follow-up visit will occur 90 days after the last dose or before the start of the next anti-lymphoma therapy.

The clinical Q12W follow-up (visits every 12 weeks, calendar days starting from cycle 1 day 1) will occur after the participant ends treatment and will continue until disease progression, withdrawal of consent, loss to follow-up, death, start of next anti-lymphoma treatment, or end of study, whichever is earlier. The first Q12W follow-up visit will occur on the next planned Q12W efficacy assessment after end of treatment is determined. This period only applies to participants who discontinue study treatment for reasons other than disease progression.

Participants who discontinue from clinical follow-up but have not withdrawn consent will continue survival follow-up until death, loss to follow-up, withdrawal of consent, or study termination by the sponsor, whichever is earlier. Participants may be followed remotely for survival follow-up.

The sponsor has the right to terminate the study at any time.

6.1.2. Description of Dose De-escalation

Dose Levels- Part 1 (Safety Run-in)

Table 4 provides the dosing schema of odronextamab in Part 1 (Safety Run-in).

Dosing will commence with the recommended phase 2 dose (RP2D) of odronextamab monotherapy (80 mg) for FL, DL1. If DL1 is not tolerated, the sponsor will examine a lower dose DL-1, as shown in Table 4.

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Table 4: Odronextamab Dose De-Escalation Schema

Dose Level (DL)	Odronextamab Dose					
	Initial dose	**Intermediate dose 1**	**Intermediate dose 2**	**Full dose**	**2x full dose**	**Q8W Maintenance dose**
	Cycle 1			**Cycle 2 to 4**	**Cycle 5 & 6**	**Cycle 7 to 18**
1	QW 0.7 mg (split 0.2/0.5)	QW 4 mg (split 2/2)	QW 20 mg (split 10/10)	80 mg	160 mg	320 mg
-1	QW 0.7 mg (split 0.2/0.5)	QW 4 mg (split 2/2)	QW 20 mg (split 10/10)	40 mg	80 mg	320 mg

The safety evaluation will be based on the Bayesian Optimal Interval Design (BOIN) with a target DLT rate of 28%. Target intervals used for calculation of the boundaries 0.221 and 0.334 in Table 5 included e.g. 0.6*0.28, and 1.4*0.28. Six to 12 participants will be enrolled in each dose level. At least 12 DLT-evaluable participants must be enrolled in the dose level selected for Part 2 before proceeding to Part 2; after the first participant is dosed, there will at least be a 24 hour wait period for dosing the second participant. For the decision on de-escalation or re-escalation, at least 6 DLT-evaluable participants are needed. The decision rule is provided in Table 5.

Table 5: Decision Rule at the Current Dose Level with Target DLT Rate 28%

Action	Number of DLT-evaluable participants treated at the current dose											
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Escalate if DLT rate ≤0.221 or if # of DLT ≤	0	0	0	0	1	1	1	1	1	2	2	2
De-escalate if DLT rate ≥0.334 or if # of DLT ≥	1	1	2	2	2	3	3	3	4	4	4	5

DLT=dose-limiting toxicity
DLT rate for a dose level is calculated by the number of participants with DLTs divided by the number of DLT-evaluable participants in the dose level.

Step 1: Enroll 6 participants in DL1.

- If DLT rate ≤ 0.221 out of the first 6 DLT-evaluable participants, enroll 6 additional participants at DL1.
  a. If DLT rate ≤ 0.221 out of the 12 DLT-evaluable participants, conclude this to be the recommended dose and proceed to Part 2.
  b. If DLT rate ≥ 0.334 out of the 12 participants, stop enrollment at DL1, perform safety review, and consider de-escalating to DL-1.
  c. If 0.221 < DLT rate < 0.334 out of the 12 DLT-evaluable participants, because the maximum sample size has been reached for the dose level, the decision on

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whether to proceed to Part 2 with this dose will be made based on the review of overall safety and PK data.

- If DLT rate ≥ 0.334 out of the first 6 DLT-evaluable participants, stop enrollment at DL1, perform safety review, and consider de-escalating to DL-1.
- If 0.221 < DLT rate < 0.334 out of the first 6 participants, enroll 6 additional participants at DL1.
    a. If DLT rate ≤ 0.221 out of the 12 DLT-evaluable participants, conclude this to be the recommended dose and proceed to Part 2.
    b. If DLT rate ≥ 0.334 out of the 12 participants, stop enrollment at DL1, perform safety review, and consider de-escalating to DL-1.
    c. If 0.221 < DLT rate < 0.334 out of the 12 DLT-evaluable participants, because the maximum sample size has been reached for the dose level, the decision on whether to proceed to Part 2 with this dose will be made based on the review of overall safety and PK data.

Step 2: If de-escalating to DL-1, enroll 6 participants.

- If DLT rate ≤ 0.221 out of the first 6 DLT-evaluable participants, re-escalate to DL1.
- If DLT rate ≥ 0.334 out of the first 6 DLT-evaluable participants, stop enrollment at DL-1 and perform safety review. A lower dose may be evaluated.
- If 0.221 < DLT rate < 0.334 out of the first 6 DLT-evaluable participants, enroll 6 additional participants at DL-1.
    a. If DLT rate ≤ 0.221 out of the 12 participants, re-escalate to DL1.
    b. If DLT rate ≥ 0.334 out of the 12 participants, stop enrollment at DL-1 and perform safety review. A lower dose may be evaluated.
    c. If 0.221 < DLT rate < 0.334 out of the 12 DLT-evaluable participants, because the maximum sample size has been reached for the dose level, the decision on whether to proceed to Part 2 with this dose will be made based on the review of overall safety and PK data.

Step 3: If re-escalating to DL1, enroll 6 participants and repeat Step 1 until the maximum sample size is exhausted.

The actual number of DLT-evaluable participants per dose level may be variable. The decision rule during the study will depend on the number of evaluable participants at each dose level and the observed number of DLTs.

In the event that DL-1 is selected, 8 additional participants will be enrolled in this dose level. The safety and efficacy of at least 20 participants treated at DL-1 (including 12 participants from the BOIN evaluation) with adequate follow up will be evaluated to support the proposed dose prior to the initiation of Part 2.

6.1.3. Dose-Limiting Toxicities

A DLT will be defined as any of the toxicities listed below unless the event is clearly attributable to the underlying disease or to an extraneous cause (including concomitant medications). To be DLT-evaluable, a participant must have completed the DLT observation period of 35 days or have

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received at least 2 full doses of odronextamab or have experienced a DLT. The DLT observation period will start with the first dose of odronextamab. If a dose is delayed during the DLT observation period, the DLT observation period will be extended by 7 days (total of 42 days).

The following TEAEs occurring during the DLT observation period will be considered a DLT:

Non-Hematologic Toxicity:

- Grade 5 non-hematological toxicity
- Any grade seizure
- Grade 4 ALT/AST values sustained for >3 consecutive days
- Grade ≥4 tumor lysis syndrome (TLS)
- Any other grade ≥3 toxicity, except:
  - Alopecia
  - Fatigue
  - Nausea, vomiting, or diarrhea lasting <72 hours with supportive measures as prescribed by the treating physician
  - Grade 3 infusion-related reaction (IRR) or CRS that responds to medical management and acute effects resolve to grade 1 or baseline within 72 hours. Note: In the context of clinical CRS or IRR, lab abnormalities for AST and ALT can be at same grade for ≥7 days provided there is no suggestion of persistent organ injury.
  - Following isolated laboratory abnormalities in the absence of clinical symptoms: alkaline phosphatase (ALP), gamma glutamyl transferase, amylase, lipase, international ratio (INR), activated partial thromboplastin time (aPTT), hypertriglyceridemia, and electrolyte abnormalities, where hospitalization is not indicated.

Hematologic Toxicity:

- Any grade 5 hematologic toxicity
- Grade 4 neutropenia lasting >7 days despite granulocyte colony stimulating factor (G-CSF)
- Grade 4 neutropenia with documented infection
- Grade 4 febrile neutropenia
- Grade 4 thrombocytopenia lasting >7 days
- Grade ≥ 3 thrombocytopenia associated with grade ≥ 2 bleeding (except for grade 2 epistaxis)

Treatment-emergent adverse events (TEAEs that appear to meet the DLT definition will be discussed between the sponsor and the investigator). The final decision regarding whether the

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TEAE meets the DLT definition will be based on review of all relevant data by the sponsor. The investigator will also be consulted.

Participants who experience a protocol-defined DLT will be required to temporarily discontinue treatment. The DLT event will be further assessed and managed, and these participants may resume study treatment once the toxicity resolves to grade 1 or baseline, or when the toxicity is stable and manageable with ongoing supportive/medical therapy. Resumption of odronextamab treatment after the initial or recurrent hematologic and non-hematologic toxicities (other than CRS, IRR, ICANS or TLS) should be at the dose, based upon the guidance outlined in Table 13 and Table 14.

DLT Observation Period

The DLT observation period is defined as the first 35 days starting from cycle 1 day 1 (first odronextamab administration) up to 2 full doses. If a dose is delayed during the DLT observation period, the DLT observation period will be extended by 7 days (total of 42 days).

6.1.4. Study Pausing Rules for Part 1 and Part 2

Evaluation of safety events will occur during the entire duration of study. For odronextamab given at any dose level, the enrollment will be paused if participants experience any of the following toxicities at a rate higher than specified below (see Table 6, Table 7, and Table 8). Such events will be reviewed by the Sponsor and IDMC. For the first 10 participants in Part 1, the stopping rules will be triggered when any of the following criteria are met:

- If 2 or more participants have grade 4 CRS events
- If 2 or more participants have grade 4 treatment-related ICANS events
- Any treatment-related non-infectious fatal events

Furthermore, once more than 10 participants have been treated in Part 1, toxicity criteria and respective rates for enrollment-pause and review of events are as follows:

- For grade 4 CRS – if the lower bound of the 1-sided 80% confidence interval of the incidence rate exceeds 4% (Table 6)
- For grade 4 treatment-related ICANS – if the lower bound of the 1-sided 80% confidence interval of the incidence rate exceeds 4% (Table 6)
- For treatment-related, life-threatening non-hematologic AEs – if the lower bound of the 1-sided 80% confidence interval of the incidence rate exceeds 20% (Table 7)
- For treatment-related fatal events – if the lower bound of the 1-sided 80% confidence interval of the incidence rate exceeds 3% (Table 8)

Table 6: Stopping Boundaries to Pause Enrollment for Grade 4 CRS or Treatment-Related Grade 4 ICAN

Number of Participants Treated	Number of Participants with any Trigger Event Leading to Pause
10-21	≥2
22-32	≥3

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Table 7: Stopping Boundaries to Pause Enrollment for Treatment-Related, Life-threatening, Non-hematologic AEs

Number of Participants Treated	Number of Participants with any Trigger Event Leading to Pause
10-12	≥4
13-17	≥5
18-21	≥6
22-25	≥7
26-29	≥8
30-32	≥9

Table 8: Stopping Boundaries to Pause Enrollment for Treatment-Related Fatal Events

Number of Participants Treated	Number of Participants with any Trigger Event Leading to Pause
10-28	≥2
29-32	≥3

During the pause, all available data for participants who received study treatment will be reviewed, dose selection will be re-evaluated, and dose reduction will be considered based on the benefit-risk assessment of all participants treated. Safety data will be reviewed on an ongoing basis throughout the trial. Re-initiation of dosing after a pause will be by study amendment except in the case where the AE that prompted the pause is downgraded by the investigator such that the study pause condition is no longer present. During Part 2, the unblinded safety review will be performed by the IDMC and the enrollment pause recommendation will be based on the comparative assessment of the safety events in both treatment arms.

6.1.5. End of Study Definition

The definition for End of Study (Trial) is the date of global last participant's last visit, the date of withdrawal from the study, or lost to follow-up (ie, the study participant can no longer be contacted by the investigator).

6.2. Planned Interim Analysis

After the primary analysis of CR30, one formal interim efficacy analysis of PFS is planned using Lan-DeMets O'Brien-Fleming spending function, when approximately 130 PFS events (75% of total events) are observed. A formal interim efficacy analysis of EFS will also be performed at the time of the PFS interim efficacy analysis. The details are provided in Section 11.5.

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6.3. Study Committees

6.3.1. Steering Committee

The conduct of this trial will be overseen by a scientific steering committee (SSC), presided over by the coordinating principal investigator and, if possible, the representative regional investigators from countries participating in this study. The SSC will serve in an advisory capacity to the sponsor. Operational details for the SSC will be detailed in a separate SSC charter.

Note: The SSC is separate from the Independent data monitoring committee (IDMC).

6.3.2. Independent Data Monitoring Committee

Members who are independent from the sponsor and the study investigators will compose an IDMC that will monitor participant safety and efficacy by conducting formal reviews of accumulated data by treatment group during the course of the study.

The IDMC will provide the sponsor with appropriate recommendations on the conduct of the clinical study to ensure the protection and safety of the participants enrolled. The IDMC will also institute any measures required for ensuring the integrity of the results during the study.

The first IDMC will commence after 30 randomized participants (approximately 15 in each arm) in study Part 2 have completed cycle 1. The IDMC will meet and review the totality of safety data (from Part 1 and Part 2).

The IDMC will monitor the data throughout Part 2 to ensure participant safety by conducting regular periodic reviews of safety data, and ensure that benefit/risk remains favorable for study participant, during the course of the study.

The details, including IDMC members, their roles, responsibilities, and the meeting frequency, can be found in the IDMC charter.

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7. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PARTICIPANTS

7.1. Number of Participants Planned

A maximum total of 478 participants are planned to be enrolled across Parts 1 and 2.

In Part 1, a minimum of 12 and a maximum of 32 participants are planned to be enrolled.

In Part 2, an estimated 446 participants (approximately 223 participants in each treatment arm) will be enrolled.

7.2. Study Population

The study population will consist of participants of 18 years and older with previously untreated $CD20^+$ FL based on World Health Organization (WHO) classification.

The investigator must ensure that all eligibility criteria stated in the protocol that were met at the time of screening continue to be met up to the time of administration of the first dose on cycle 1 day 1.

7.2.1. Inclusion Criteria

A participant must meet the following criteria to be eligible for inclusion in the study:

1. **Have diagnosis of $CD20^+$ FL Grade 1-3a, stage II bulky or stage III / IV:** Local histopathologic confirmation of the $CD20^+$ FL Grade 1 to 3a, must be obtained before study enrollment. Biopsies must have been obtained within 18 months prior to study enrollment. A corresponding tumor biopsy sample should be submitted to the central laboratory.
    a. **For Part 1 (Safety Run-In) only:** FLIP1 score of 3 to 5.
2. Need for treatment as indicated: Presence of ≥1 of the following: B symptoms, large tumor mass (characterized by lymphomas with a diameter >3 cm in 3 or more regions or by a lymphoma with a diameter >6 cm in 1 region), and/or presence of lymphoma-related complications.
3. Have measurable disease on cross-sectional imaging documented by diagnostic imaging CT or MRI (measurable disease is defined as at least 1 bidimensionally measurable nodal lesion of >1.5 cm or extranodal disease of >1 cm in the greatest transverse diameter (GTD) regardless of the short axis diameter).
4. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2.
5. Male or female ≥ 18 years of age or the legal age of adults to consent to participate in a clinical study per country-specific regulations, whichever is greater, at the time of consent.
6. Adequate bone marrow function as documented by:
    a. Platelet count ≥ 50 x 10^9/L. A participant may not have received platelet transfusion therapy within 7 days prior to first dose of odronextamab in order to meet the platelet eligibility criterion.

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b. Hemoglobin ≥ 9.0 g/dL
c. Absolute neutrophil count (ANC) ≥ 1.0 x 10^9/L. A participant may not have received G-CSF within 2 days prior to the first dose of odronextamab in order to meet the ANC eligibility criterion.
d. Participants with bone marrow involvement or splenic sequestration should meet the following hematologic parameters:

   - Platelet count ≥ 25 x 10^9/L. A participant may not have received platelet transfusion therapy within 3 days prior to first dose of odronextamab in order to meet the platelet eligibility criterion.
   - Hemoglobin ≥ 7.0 g/dL
   - ANC ≥ 0.5 x 10^9/L. A participant may not have received G-CSF within 2 days prior to first dose of odronextamab in order to meet the ANC eligibility criterion.

7. Participants with adequate hepatic function:

   a. Total bilirubin ≤ 1.5 × upper limit of normal (ULN) (≤3 × ULN if attributed to lymphoma infiltration of liver).
   b. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × ULN (≤5 × ULN if attributed to lymphoma infiltration of liver).
   c. Alkaline phosphatase (ALP) ≤ 2.5 × ULN (≤5 × ULN if attributed to lymphoma infiltration of liver).
   NOTES:
   * Irrespective of the presence of lymphoma infiltration of the liver, a participant with an AST >2.5 x ULN and/or ALT > 2.5 x ULN concurrent with a total bilirubin > 1.5 x ULN will be excluded.
   * Participants with known Gilbert syndrome will be excluded if the total bilirubin value is >4 x ULN for the local general population.

8. Calculated creatinine clearance by Cockcroft-Gault formula ³ 50 mL/min.

   NOTE: Participants with a calculated creatinine clearance < 50 mL/min may be considered for enrollment if a measured creatinine clearance (based on 24-hour urine collection or other reliable method) is ≥50 mL/min.

9. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information by study participant.
10. Willing and able to comply with clinic visits and study-related procedures.
11. Able to understand and complete study-related questionnaires.

7.2.2. Exclusion Criteria

A participant who meets any of the following criteria will be excluded from the study:

1. Participants with central nervous system (CNS) lymphoma or leptomeningeal lymphoma.
   a. Primary CNS lymphoma or known involvement by non-primary CNS lymphoma (even if treated into complete remission).

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   b. Suspected CNS involvement by lymphoma must be evaluated by CNS imaging (MRI or CT) and by lumbar puncture as appropriate.

2. Participants with histological evidence of transformation to a high-grade or diffuse large B-cell lymphoma.
3. Participants with Waldenström macroglobulinemia (WM, lymphoplasmacytic lymphoma), Grade 3b follicular lymphoma, chronic lymphocytic leukemia, or small lymphocytic lymphoma.
4. Treatment with any systemic anti-lymphoma therapy.
5. Recent major surgery (within 4 weeks prior to the start of assigned study treatment).
6. Standard radiotherapy within 14 days of first administration of assigned study treatment.
7. History of solid organ transplantation.
8. Continuous systemic corticosteroid treatment with more than 10 mg per day of prednisone/prednisolone or anti-inflammatory equivalent within 72 hours of start of study drug.
9. A malignancy other than NHL unless the participant is adequately and definitively treated and is cancer free for at least 3 years with the exception of localized prostate cancer treated with hormone therapy or local radiotherapy (i.e. pellets), cervical carcinoma in situ, breast cancer in situ, or nonmelanoma skin cancer that was definitively treated.
10. Any other significant active disease or medical condition that could interfere with the conduct of the study or put the participant at significant risk, including but not limited to significant cardiovascular disease (eg, New York Heart Association Class III or IV cardiac disease, myocardial infarction within the previous 6 months, unstable arrhythmias, or unstable angina); significant pulmonary disease (eg, obstructive pulmonary disease and history of symptomatic bronchospasm); or gastrointestinal, hepatic, renal, endocrine, hematologic, autoimmune, psychiatric, or neurologic disorder.
11. History of or current relevant CNS pathology, such as epilepsy, seizure, paresis, aphasia, apoplexy, severe brain injury, cerebellar disease, organic brain syndrome, psychosis, inflammatory lesions, and/or vasculitis.
12. Vaccination within 28 days prior to first study drug administration with a vector that has replicative potential.
13. Cardiac ejection fraction <50% by echocardiogram or multigated acquisition (MUGA) scan.
14. Pregnant or breastfeeding women.
15. Women of childbearing potential (WOCBP)* or men who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 6 months after the last dose. Sperm donation is prohibited during the study and for 6 months after the last dose of study drug. Highly effective contraceptive measures include:

a. stable use of combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening;
b. intrauterine device (IUD); intrauterine hormone-releasing system (IUS);
c. bilateral tubal occlusion/ligation;
d. vasectomized partner (provided that the male vasectomized partner is the sole sexual partner of the WOCBP study participant and that the vasectomized partner has obtained medical assessment of surgical success for the procedure); and/or
e. sexual abstinence**.

NOTE: Pregnancy testing and contraception are required for WOCBP. Pregnancy testing and contraception are not required for women who are post-menopausal or permanently sterile.

*WOCBP are defined as women who are fertile following menarche until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient to determine the occurrence of a postmenopausal state. The above definitions are according to the Clinical Trial Facilitation Group (CTFG) guidance.

**Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drugs. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.
Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception. Female condom and male condom should not be used together.

16. History of clinically significant cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, psychiatric, or neurological disease, as assessed by the investigator, that may confound the results of the study or poses an additional risk to the participant by study participation.
17. Has a history of tuberculosis or systemic fungal diseases that has been active within 6 months.
18. Infections:

- Infection requiring hospitalization or treatment with IV anti-infectives within 2 weeks of first administration of assigned study treatment. There should be evidence that the infection has cleared or is well controlled by start of study therapy.
- Evidence of any active infection (bacterial, viral, fungal, mycobacterial, parasitic, or other) at study enrollment or within 2 weeks of study enrollment, if requiring ongoing

treatment and/or has the potential to cause disseminated disease or severe infection upon immunosuppression.

- Active COVID-19 infection defined as PCR^+
- Uncontrolled infection with human immunodeficiency virus (HIV), hepatitis B (HBV), or hepatitis C (HCV).
- Cytomegalovirus (CMV) infection as noted by detectable levels on peripheral blood PCR assay. Participants who show detectable levels of CMV at screening will need to be treated with appropriate antiviral therapy and demonstrate at least 2 undetectable levels of CMV by PCR assay (at least 7 days apart) before being re-considered for eligibility.

NOTE: Participants with HIV who have controlled infection (undetectable viral load and CD4 count above 350 cells/µL either spontaneously or on a stable antiviral regimen) are permitted.

NOTE: Participants who are hepatitis B surface antigen positive or who are hepatitis B core antibody positive should undergo evaluation by a specialist and be considered for antiviral prophylaxis, before they are permitted onto study.

NOTE: Participants who are hepatitis C virus antibody positive (HCV Ab+) who have controlled infection (undetectable HCV RNA by PCR either spontaneously or in response to a successful prior course of anti-HCV therapy) are permitted.

19. Allergy/hypersensitivity:
    a. History of severe allergic reaction attributed to compounds with a similar chemical or biologic composition as that of the study drug or excipient.
    b. Known hypersensitivity to both allopurinol and rasburicase.
20. Participated in any clinical research study evaluating another investigational drug including biologics or therapy, including specific immunotherapy, within 90 days or at least 5 half-lives (whichever is longer) of an investigational biologic drug, or at least 4 weeks for other investigational drug, prior to the screening visit.
21. Participants who are committed to an institution by virtue of an order issued either by the judicial or the administrative authorities.

7.3. Premature Withdrawal from the Study

A participant has the right to withdraw from the study at any time, for any reason, and without repercussion.

The investigator and/or sponsor have the right to withdraw a participant from the study if it is no longer in the interest of the participant to continue in the study or if the participant's continuation in the study places the scientific outcome of the study at risk (eg, if a participant does not or cannot follow study procedures). An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of participants should be avoided.

Rules for discontinuation of study treatment (permanent or temporary) are discussed in Section 8.3.3.

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7.4. Replacement of Participants

During study Part 1 (Safety Run-in), participants enrolled and withdrawn from the study any time prior to the first dose of study drug will not be considered evaluable for assessment and will be replaced with another participant. In addition, during Part 1, participants who are not considered DLT-evaluable will be replaced with another participant.

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8. STUDY TREATMENTS

8.1. Investigational and Comparator Treatments

Table 9 describes study interventions administered in this study.

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Table 9: Study Interventions Administered

Intervention Label	**Arm 1**	**Arm 2**					
Intervention Name	**Odronextamab**	**Rituximab**	**Cyclophosphamide**	**Doxorubicin**	**Vincristine**	**Prednisone/ Prednisolone**	**Bendamustine**
Dose Formulation	Sterile solution	Sterile solution	Sterile solution	Sterile solution	Sterile solution	Tablet/Capsule	Sterile Solution
Unit Dose Strength(s)	2 mg/mL and 20 mg/mL	IV: 100 mg/10 mL, 500 mg/50 mL SC: 1,400 mg rituximab and 23,400 Units hyaluronidase human per 11.7 mL (120 mg/2,000 Units per mL) solution	Varies by country	Varies by country	Varies by country	Varies by country	Varies by country
Dosage Level(s)	See Section 8.1.1	See Section 8.1.2	750 mg/m^2 IV; see Section 8.1.3	50 mg/m$^{2;}$ see Section 8.1.3	1.4 mg/m^2 see Section 8.1.3	100 mg, see Section 8.1.3	90 mg/m^2, see Section 8.1.3
Route of Administration	IV infusion	IV infusion or SC	IV	IV	IV	PO	IV
Use	Experimental	Active comparator	Active comparator	Active comparator	Active comparator	Active comparator	Active comparator
IMP/AxMP	IMP	IMP	IMP	IMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor or locally by the study site	Provided centrally by the sponsor or locally by the study site	Provided centrally by the sponsor or locally by the study site	Provided centrally by the sponsor or locally by the study site	Provided centrally by the sponsor or locally by the study site	Provided centrally by the sponsor or locally by the study site
Packaging and Labeling	Provided in sterile single-use vials. Each vial will be labeled as required per country requirements.	Provided as vials in cartons. Each will be labeled as required per country requirements.	Provided as vials in cartons. Each will be labeled as required per country requirements.	Provided as vials in cartons. Each will be labeled as required per country requirements.	Provided as vials in cartons. Each will be labeled as required per country requirements.	Provided as blisters/bottles. Each will be labeled as required per country requirements	Provided as vials in cartons. Each will be labeled as required per country requirements.

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Odronextamab dose administered is a flat dose and not dependent on participant weight or body surface area. Detailed preparation and administration instructions for odronextamab will be provided to the sites in the study pharmacy manual. Detailed preparation and administration instructions for the investigator's choice chemotherapy should be in accordance with the product's package insert.

A pharmacist or other qualified individual will be identified at each site to prepare all study drugs for administration.

8.1.1. Odronextamab Dose and Administration

During the induction treatment period, odronextamab will be administered IV with step-up dosing in cycle 1 to mitigate the risk for CRS. Cycle 1 will consist of an initial dose of 0.7 mg (split as 0.2 mg on cycle 1 day 1 and 0.5 mg on cycle 1 day 2), an intermediate dose 1 of 4 mg (split as 2 mg on cycle 1 day 8 and 2 mg on cycle 1 day 9), and an intermediate dose 2 of 20 mg (split as 10 mg on cycle 1 day 15 and 10 mg on cycle 1 day 16).

From cycle 2 to cycle 4, odronextamab will be administered IV on days 1, 8, and 15 at 80 mg, and from cycle 5 and cycle 6, odronextamab will be administered IV at 160 mg on day 8 in cycle 5 and days 1 and 15 in cycle 6 (Table 10). Each cycle from cycle 1 to cycle 6 consists of 21 days.

During the monotherapy maintenance treatment period, odronextamab will be administered IV Q8W at 320 mg (Table 10). The first dose of odronextamab (320 mg) during maintenance will be administered 6 weeks after the last dose (160 mg) given during induction on cycle 6 day 15.

Table 10: Odronextamab Administration

Odronextamab Dose Regimen									
Cycle 1 Day 1	**Cycle 1 Day 2**	**Cycle 1 Day 8**	**Cycle 1 Day 9**	**Cycle 1 Day 15**	**Cycle 1 Day 16**	**Cycle 2 - 4 Day 1, 8 and 15**	**Cycle 5 Day 8**	**Cycle 6 Day 1 and 15**	**M1 to M12 Day 1**
Initial (0.7 mg)		**Intermediate 1 (4 mg)**		**Intermediate 2 (20 mg)**		**Full dose**	**2x full dose**	**2x full dose**	**Maintenance Q8W**
0.2 mg	0.5 mg	2 mg	2 mg	10 mg	10 mg	80 mg	160 mg	160 mg	320 mg

For the initial dose, intermediate dose 1, and intermediate dose 2, the treatment will be split into 2 separate infusions given on 2 separate days, which are preferably consecutive but no more than 3 days apart. Each of the split infusions during cycle 1 and the first full dose QW infusion (cycle 2 day 1) should occur over 4 hours. Subsequent treatments may be administered as a single infusion or as 2 separate infusions and may be administered over at least 1 hour depending on tolerability.

Due to the risk for CRS, participants must be closely monitored for at least 24 hours (± 4 hours) beyond the end of each split infusion during cycle 1 (step-up dosing); see Section 9.2.3.1 for details. Starting from C2D1 (first full dose) of odronextamab, close monitoring for observation of CRS signs and symptoms is no longer required, unless the participant experienced a prior CRS event.

Participants at risk for TLS will be monitored according to the TLS risk-monitoring schedule as specified in Section 8.4.4.

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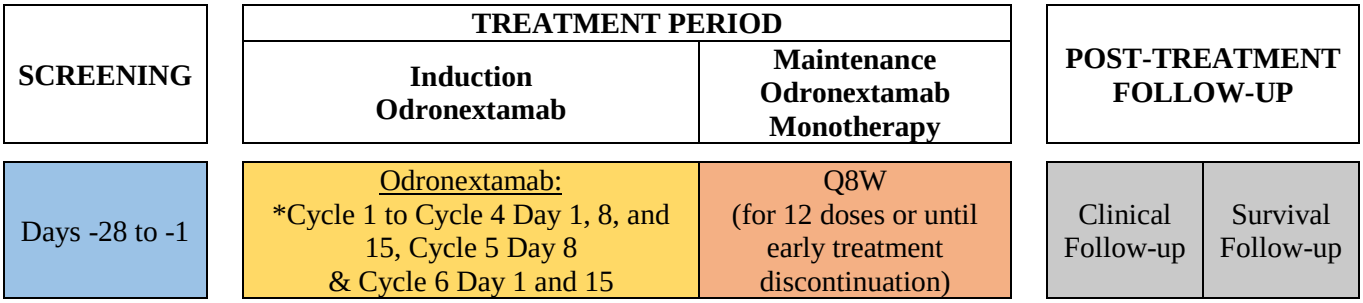
Premedications to mitigate the risk and reduce the severity of CRS are detailed in Section 8.2.1.

Figure 4 illustrates the participant level study flow and study treatment periods for participants receiving odronextamab, assuming there are no delays in dosing. Participants will receive 6 cycles of odronextamab on a 21-day schedule. Participants will receive odronextamab with step-up dosing (as per Table 10). Six weeks after the dose on cycle 6 day 15, participants (who had CR or PR) will start the maintenance treatment period of odronextamab monotherapy on a Q8W schedule.

Figure 4: Odronextamab Participant-Level Study Flow Diagram



*Cycle 1 splits the step-up doses over 2 consecutive days: cycle 1 day 1/day 2, day 8/day 9, and day 15/day 16.

8.1.2. Rituximab

For this study, use of rituximab or biosimilars is permitted. Rituximab must be administered according to institutional guidelines or according to the instructions in the product package insert.

For the duration of treatment of a given patient, the same formulation should be used.

For details about rituximab, including formulation and administration, please verify the product package insert.

8.1.2.1. Dose and Administration

Rituximab will be administered IV on day 1 of each cycle in a dose of 375 mg/m^2. For SC administration, the dose is 1,400 mg/23,400 Units (1,400 mg rituximab and 23,400 Units hyaluronidase human). All patients must receive at least one full dose of a rituximab product by intravenous infusion before receiving subcutaneous rituximab injection. For the duration of treatment for a given participant, after the first dose, the same route of administration should be used. If clinically indicated, switching between routes of administration will be permitted after discussion with the medical monitor.

The frequency and duration of rituximab will be Q3W in combination with induction chemotherapy (CHOP/CVP) for 6 cycles of 21 days each and Q4W with induction bendamustine for 6 cycles of 28 days each (induction treatment phase). Upon completion of the combination treatment period or early termination of chemotherapy, rituximab will be continued as monotherapy Q8W for up to 12 maintenance doses (if participant has CR or PR), unless the participant discontinues early due to toxicity, progressive disease, or start of subsequent lymphoma therapy or due to discretionary reasons (participant or investigator).

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8.1.3. Rituximab-Chemotherapy Combination Dosing

Figure 5 illustrates the participant-level study flow, and treatment periods for participants receiving rituximab and chemotherapy administration is described in Table 11. For details about CHOP/CVP and bendamustine, including formulation and administration, refer to the product package insert. Eight weeks after the dose on cycle 6 day 1, participants (who had CR or PR) will start the maintenance treatment period of rituximab monotherapy on a Q8W schedule.

Figure 5: Rituximab-Chemotherapy Participant-Level Study Flow Diagram

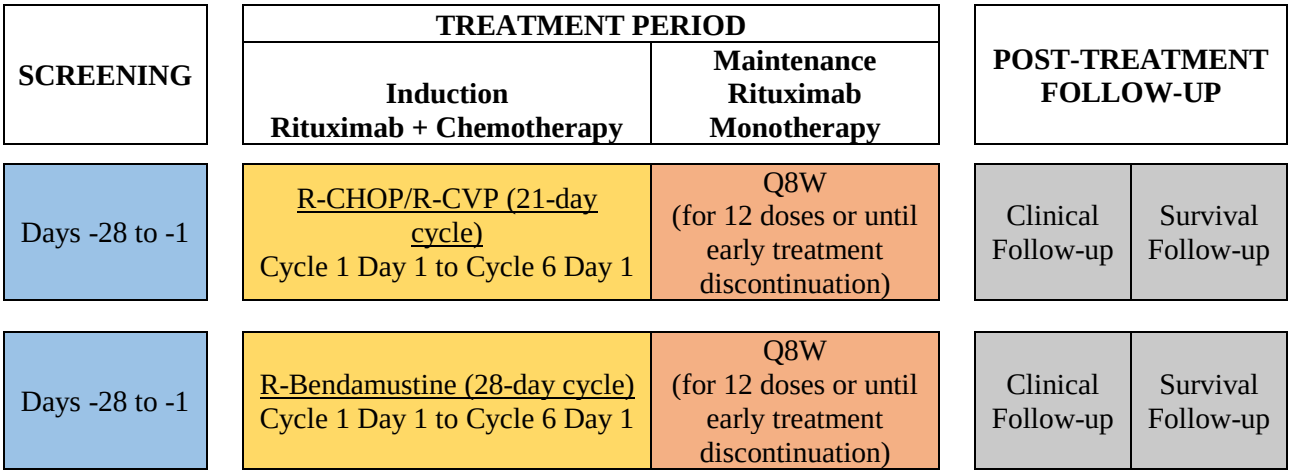

Table 11: CHOP/CVP and Bendamustine Dose

Investigator's Choice Arm	Drug	Dose	Route	Days	Cycle Length (Days)/ # of cycles
CHOP (Bartlett, 2019)	Cyclophosphamide	750 mg/m^2	IV	1	21 days / 6 cycles
	Doxorubicin	50 mg/m^2	IV	1	21 days / 6 cycles
	Vincristine	1.4 mg/m^2 (max 2 mg)	IV	1	
	Prednisone/prednisolone	100 mg	PO	1-5	
CVP	Cyclophosphamide	750 mg/m^2	IV	1	21 days / 6 cycles
	Vincristine	1.4 mg/m^2 (max 2 mg)	IV	1	21 days / 6 cycles
	Prednisone/prednisolone	100 mg	PO	1-5	
Bendamustine	Bendamustine	90 mg/m^2	IV	1-2	28 days/6 cycles

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8.2. Pretreatment

8.2.1. Premedication for Odronextamab

To mitigate the risk and reduce the severity of CRS, prior to each administration of odronextamab until the first assigned full weekly dose (planned at cycle 2 day 1), participants must receive premedication including dexamethasone, antihistamine, and acetaminophen as described below. Additionally, it is recommended that gastrointestinal (GI) prophylaxis is considered against peptic ulcer disease when a participant is on corticosteroids during the step-up dosing and first assigned full weekly dose period, as standard of care.

Premedication with dexamethasone administered at least 1 hour prior but not more than 3 hours prior to the odronextamab infusion is required for the initial, both intermediate, and first full weekly dose, at doses specified below.

The following premedications apply to odronextamab from the initial dose up to the first full weekly dose (i.e. cycle 2 day 1). If the participant experiences CRS of any grade with the first full weekly dose, continue premedications until the full dose is tolerated without experiencing CRS:

1. **12 to 24 hours prior to planned start time of infusion:**
    a. Dexamethasone 10 mg PO or equivalent dose of steroid
2. **On the day of IV infusion during step-up dosing and first full weekly dose of odronextamab:**
    a. Dexamethasone 20 mg IV 1 to 3 hours prior to start infusion on the day of treatment
    b. Diphenhydramine 25 mg IV or PO 30 to 60 minutes before start of infusion (can be replaced with another equivalent antihistamine)
    c. Acetaminophen 650 mg PO 30 to 60 minutes before start of infusion, unless the participant has received it within the past 4 hours prior to start of infusion of odronextamab or is allergic to acetaminophen
3. **24 (±4) hours from the end of odronextamab infusion during step-up dosing and first full weekly dose of odronextamab:**
    a. Dexamethasone 10 mg PO or equivalent dose of steroid

First dose administration following full weekly dose (i.e. cycle 2 day 8) administered without experiencing CRS of any grade with 20 mg of dexamethasone IV

4. **Premedication for day of IV infusion of odronextamab following first full weekly dose:**
    a. Dexamethasone 10 mg IV 1 to 3 hours prior to start of infusion on the day of treatment
    b. Diphenhydramine 25 mg IV or PO 30 to 60 minutes before start of infusion (can be replaced with another equivalent antihistamine)
    c. Acetaminophen 650 mg PO 30 to 60 minutes before start of infusion, unless the participant has received it within the past 4 hours prior to start of infusion of odronextamab or is allergic to acetaminophen

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For subsequent doses, no premedication is required if the IV infusion is tolerated without experiencing CRS of any grade with the reduced 10 mg of dexamethasone IV.

NOTE:

Equivalent dose of steroid includes prednisone/prednisolone 60 mg or methylprednisolone 50 mg (PO dose only).

Additional premedication with antihistamines, acetaminophen, and/or nonsteroidal anti-inflammatory drugs (NSAIDs) may also be considered.

8.2.2. For Rituximab

For details about pretreatment requirement for rituximab, refer to the product-approved label.

8.3. Dose Modification and Study Treatment Discontinuation Rules

Odronextamab has a distinct safety profile and, toxicities that may be observed during use are discussed in sections below.

For dose modifications and study treatment discontinuations rules for rituximab and chemotherapy, please refer to the approved labels.

8.3.1. Odronextamab Dose Modification

During study Part 1 (Safety Run-in), participants who experience protocol-defined DLTs will be required to temporarily discontinue treatment. Such participants may be considered for continued treatment once the toxicity either resolves to grade 1 or baseline or the toxicity is stable and manageable through supportive therapy (eg, participants with well-controlled hypertension that remains at grade 3 due to the need for 2 anti-hypertensive agents). Regardless of whether a participant remains on study treatment and/or on study, such events will count toward the DLTs for the involved cohort during the dose-finding portion of the trial. Upon occurrence of a DLT or other study treatment-related event at any dose regimen and at any time on the study, continued treatment with a modified dose of odronextamab is allowed at the discretion of the investigator and sponsor.

Table 12 below provides guidelines for dose modification in the event of hematologic toxicities and non-hematologic toxicities other than CRS, IRR, and TLS. The participant may restart treatment at the same dose or a reduced dose, if in the opinion of the investigator and the sponsor, it is in the best interest of the participant.

Odronextamab may need to be held in the event of adverse events (AEs) such as acute allergic/systemic hypersensitivity reactions, central nervous system toxicity (ICANS), CRS, TLS, and B-cell depletion and infections. Please also refer to Section 8.4.

For participants who experience CRS, refer to Table 17 for dose modification guidelines.

For participants who experience TLS, refer to Section 8.4.4.3.

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Table 12: Guidance on Odronextamab Dosing for Hematologic and Non-Hematologic Toxicities (Other than CRS, IRR, and TLS)

AE	Grade	Hold (Yes/No)	Restarting Criteria (only apply if treatment held)	Rechallenge	Discontinuation Criteria
Hematologic	1, 2, 3	No, Except for G3 events of coagulopathy* with bleeding or G3 febrile neutropenia with documented infection, odronextamab should be held	Resolves to G2 (neutropenia) or G1 or baseline	Resume odronextamab at the dose prior to the hold	Consider for any severe events that do not resolve to <G2 within 12 weeks of AE onset with appropriate therapy
	4	Yes	Resolves to G2 (neutropenia) or G1 or baseline	Resume odronextamab at the dose prior to the hold	Toxicity does not resolve to <G4 within 2 weeks of AE onset or <G2 within 12 weeks of AE onset Consider permanent discontinuation for any life-threatening event
Non-hematologic	2 (except G2 alopecia, fatigue, nausea, vomiting, diarrhea, and clinically insignificant lab abnormalities)	Consider holding for persistent concerns despite appropriate management	Resolves to G1 or baseline	Resume odronextamab at the dose prior to the hold	Toxicity does not resolve within 12 weeks of AE onset with appropriate therapy
	3	Yes	Resolves to G1 or baseline	Resume odronextamab at the dose prior to the hold.	Toxicity doesn't resolve within 12 weeks of AE onset with appropriate therapy
	4	Yes	N/A	N/A	If drug-related and life-threatening toxicity, then discontinue odronextamab, with the exception of clinically insignificant laboratory abnormalities that can resolve with supportive care.

*Coagulopathy is identified by derangement in PT, aPTT, and/or fibrinogen levels, with or without bleeding.

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8.3.1.1. Temporary Discontinuation of Odronextamab

The investigator may temporarily discontinue study drug dosing at any time even without consultation with the Regeneron medical director, if the urgency of the situation requires immediate action and if this is determined to be in the participant's best interest.

If a participant requires a prohibited medication (Section 8.8.1) at any time during the study, the principal investigator should contact the Regeneron medical director (except for illness requiring prompt treatment). Based on the discussions, study drug may be continued or temporarily or permanently discontinued.

After the condition leading to temporary discontinuation of study drug resolves, study drug dosing may resume.

Resumption of study drug dosing requires consultation and agreement between the investigator and the Regeneron medical director.

Odronextamab may need to be held in the event of AEs such as acute allergic/systemic hypersensitivity reactions, CNS toxicity (ICANS), CRS, TLS, and B-cell depletion and infections. Please also refer to Section 8.4.

For participants who experience CRS, refer to Section 8.4.2 for dose modification guidelines.

For participants who experience TLS, refer to Section 8.4.4.

For participants who had temporary treatment interruption, the sponsor should be consulted to discuss the participant's individual risk factors, such as prior history of CRS, before re-instituting study therapy per guidance in the section below.

8.3.1.2. Treatment Resumption Following Odronextamab Dose Interruption

Treatment will continue per the treatment plan until disease progression, withdrawal of consent, unacceptable toxicity, or other reasons as detailed in Section 8.3.3.1.

For participants who have temporary treatment interruption, dosing with odronextamab will be resumed following the guidelines as shown in Table 13 and Table 14:

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Table 13: Guidelines on Odronextamab Treatment Resumption During Step-Up Dosing

Day	Last dose administered	Time since the last dose administered	Action for next dose
1	0.2 mg	> 3 days	Repeat 0.2 mg (Cycle 1 Day 1), then administer 0.5 mg (Cycle 1 Day 2) and resume the planned treatment schedule.
2	0.5 mg	≤ 2 weeks	Administer 2 mg (Cycle 1 Day 8), then resume the planned treatment schedule.
		> 2 weeks	Repeat 0.2 mg (Cycle 1 Day 1), then administer 0.5 mg (Cycle 1 Day 2) and resume the planned treatment schedule.
8	2 mg	≤ 3 days	Administer 2 mg (Cycle 1 Day 9) then resume the planned treatment schedule.
		> 3 days ≤ 2 weeks	Repeat 2 mg (Cycle 1 Day 8), then administer 2 mg (Cycle 1 Day 9) and resume the planned treatment schedule.
		> 2 weeks	Repeat 0.2 mg (Cycle 1 Day 1), then administer 0.5 mg (Cycle 1 Day 2) and resume the planned treatment schedule.
9	2 mg	≤ 2 weeks	Administer 10 mg (Cycle 1 Day 15) then resume the planned treatment schedule.
		> 2 to ≤ 3 weeks	Repeat 2 mg (Cycle 1 Day 8), then administer 2 mg (Cycle 1 Day 9) and resume the planned treatment schedule.
		> 3 weeks	Repeat 0.2 mg (Cycle 1 Day 1), then administer 0.5 mg (Cycle 1 Day 2) and resume the planned treatment schedule.
15	10 mg	≤ 3 days	Administer 10 mg (Cycle 1 Day 16) then resume the planned treatment schedule.
		> 3 days ≤ 2 weeks	Repeat 10 mg (Cycle 1 Day 15), then administer 10 mg (Cycle 1 Day 16) and resume the planned treatment schedule.
		> 2 weeks ≤ 5 weeks	Repeat 2 mg (Cycle 1 Day 8), then administer 2 mg (Cycle 1 Day 9) and resume the planned treatment schedule.
		> 5 weeks	Repeat 0.2 mg (Cycle 1 Day 1), then administer 0.5 mg (Cycle 1 Day 2) and resume the planned treatment schedule.
16	10 mg	≤ 2 weeks	Administer 80 mg dose (Cycle 2 Day 1) then resume the planned treatment schedule.
		> 2 to ≤ 4 weeks	Repeat 10 mg (Cycle 1 Day 15), then administer 10 mg (Cycle 1 Day 16) and resume the planned treatment schedule.

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		> 4 to ≤ 6 weeks	Repeat 2 mg (Cycle 1 Day 8), then administer 2 mg (Cycle 1 Day 9) and resume the planned treatment schedule.
		> 6 weeks	Repeat 0.2 mg (Cycle 1 Day 1), then administer 0.5 mg (Cycle 1 Day 2) and resume the planned treatment schedule.

QW=weekly; Q2W=once every 2 weeks; Q8W=once every 8 weeks

Table 14: Guidelines on Odronextamab Treatment Resumption During Treatment Dosing

Last dose administered	Time since the last dose administered	Action for next dose
40 mg QW	≤ 3 weeks	Administer next 40 mg QW dose resume the planned treatment schedule.
	> 3 to ≤ 5 weeks	Repeat 10 mg (Cycle 1 Day 15), then administer 10 mg (Cycle 1 Day 16) and resume the planned treatment schedule.
	> 5 to ≤ 7 weeks	Repeat 2 mg (Cycle 1 Day 8), then administer 2 mg (Cycle 1 Day 9) and resume the planned treatment schedule.
	> 7 weeks	Repeat 0.2 mg (Cycle 1 Day 1), then administer 0.5 mg (Cycle 1 Day 2) and resume the planned treatment schedule.
80 mg Q2W	≤ 7 weeks	Administer next 80 mg Q2W dose then resume the planned treatment schedule.
	> 7 to ≤ 9 weeks	Repeat 10 mg (Cycle 1 Day 15), then administer 10 mg dose (Cycle 1 Day 16); administer one 40 mg dose one week prior to resumption of 80 mg Q2W.
	> 9 weeks	Repeat 0.2 mg (Cycle 1 Day 1), then administer 0.5 mg (Cycle 1 Day 2) followed by completion of step-up regimen; administer one 40 mg dose one week prior to resumption of 80 mg Q2W.
80 mg QW	≤ 5 weeks	Administer next 80 mg dose then resume the planned treatment schedule.
	> 5 to ≤ 7 weeks	Repeat 10 mg (Cycle 1 Day 15), then administer 10 mg (Cycle 1 Day 16) and resume the planned treatment schedule.
	> 7 to ≤ 10 weeks	Repeat 2 mg (Cycle 1 Day 8), then administer 2 mg (Cycle 1 Day 9) and resume the planned treatment schedule.
	> 10 weeks	Repeat 0.2 mg (Cycle 1 Day 1), then administer 0.5 mg (Cycle 1 Day 2) and resume the planned treatment schedule.
160 mg Q2W	≤ 7 weeks	Administer next 160 mg Q2W dose then resume the planned treatment schedule.
	> 7 to ≤ 10 weeks	Repeat 10 mg (Cycle 1 Day 15) then administer 10 mg (Cycle 1 Day 16); administer one 80 mg dose one week prior to resumption of 160 mg Q2W.
	> 10 weeks	Repeat 0.2 mg (Cycle 1 Day 1), then administer 0.5 mg (Cycle 1 Day 2) followed by completion of step-up regimen; administer one 80 mg dose one week prior to resumption of 160 mg Q2W.

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320 mg Q8W (40 mg QW cohort)	≤ 10 weeks	Administer next 320 mg Q8W dose.
	> 10 weeks	Repeat 0.2 mg (Cycle 1 Day 1), then administer 0.5 mg (Cycle 1 Day 2) followed by completion of step-up regimen; administer one 40 mg dose one week prior to resumption of 320 mg Q8W schedule.
320 mg Q8W (80 mg QW cohort)	≤ 10 weeks	Administer next 320 mg Q8W dose.
	> 10 weeks	Repeat 0.2 mg (Cycle 1 Day 1), then administer 0.5 mg (Cycle 1 Day 2) followed by completion of step-up regimen; administer one 80 mg dose one week prior to resumption of 320 mg Q8W schedule.

8.3.2. Modification of Investigator's Choice of Chemotherapy

Please refer to the prescribing information for rituximab/CHOP/CVP and bendamustine.

8.3.3. Study Treatment Discontinuation

Participants who permanently discontinue from study drug should be encouraged to remain in the study for the follow-up periods. Those who agree and do not withdraw consent will be asked to return to the clinic for all remaining study visits per the visit schedule.

8.3.3.1. Reasons for Permanent Discontinuation of Study Drug

Study drug dosing of an individual participant will be permanently stopped in the event of:

- Evidence of pregnancy
- Liver function test (LFT) abnormalities meeting the criteria of Hy's law:
- FDA's definition of Hy's Law includes 4 components: (1) Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation of >3× the upper limit of normal (ULN); (2) total bilirubin (TBL) elevation of > 2× ULN; (3) absence of initial findings of cholestasis (ie, absence of elevation of alkaline phosphatase [ALP] to >2× ULN); and (4) no other reason can be found to explain the combination of increased ALT and TBL, such as viral hepatitis A through E; other preexisting or acute liver disease; or another drug capable of causing the observed injury. (FDA, 2009).
- Grade 4 CRS/IRR event
- Any grade 4 non-hematological toxicity that is drug-related and life-threatening, with the exception of clinically insignificant laboratory abnormalities that can resolve with supportive measures
- Any grade TLS that does not resolve within 14 days despite appropriate management
- Grade ≥3 neurotoxicity if the signs or symptoms are attributed wholly or primarily to odronextamab treatment (See Section 8.4.3 for details)*
- Recurrent seizures of any grade
- Tuberculosis or severe uncontrolled opportunistic infections

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- Diagnosis of another malignancy during the study with the exception of localized melanoma, non-melanoma skin cancer that has undergone potentially curative therapy or in situ cervical carcinoma, or any other tumor that has been deemed to be effectively treated with definitive local control and with curative intent
- Multi-focal leukoencephalopathy
- Life-threatening allergic reactions considered related to study drug (see Section 8.4.1)
- Any medical condition that the investigator or sponsor determines may jeopardize the participant's safety if he or she continues in the study or continues treatment with study drug
- Participant withdrawal of consent at any time
- The investigator or sponsor determines it is in the best interest of the patient
- Participant non-compliance (e.g., not complying with protocol required visits, assessments, and dosing instructions)
- Start of non-protocol anti-lymphoma therapy (local radiation or surgery for palliative/symptom control only in the absence of disease progression is allowed)
- Clear evidence of progressive disease

If the participant cannot tolerate any of the assigned study treatment, they will be discontinued, and the participant will enter the post-treatment follow-up phase.

*For grade ≥3 neurotoxicity: If odronextamab treatment is considered to be a possible contributor to the CNS event but the primary etiology is judged to be other than odronextamab treatment, then study drug must be interrupted until CNS signs and symptoms resolve to grade 1 or baseline; at such a time, the study drug may be resumed at the discretion of the investigator after discussion with the sponsor. Study drug must also be interrupted in participants who experience lower grade signs or symptoms consistent with CNS toxicity, and study drug may be resumed after resolution of signs or symptoms to baseline following discussion and agreement by the investigator and the sponsor.

8.4. Safety Monitoring and Management of Specific Toxicities and Acute Reactions

Multiple measures will be taken to ensure the safety of participants in this trial. This includes stringent eligibility criteria, monitoring according to the schedule of assessments, and requirement for close monitoring during odronextamab step-up dosing.

Safety monitoring will include frequent study visits and evaluation by study staff, including physical exams, and routine and specialty laboratory testing, in addition to assessment for toxicity and AEs. Safety monitoring will include but will not be limited to vital signs (with specific attention to temperature and blood pressure), oxygen saturation, clinical assessments, and laboratory evaluations. Also, CRS/IRR events during the step-up period will be reviewed periodically by the sponsor.

Detailed management guidance for specific AEs that are anticipated such as acute allergic/hypersensitivity reactions, CRS/IRRs, and potential ICANS are provided in Section 8.4.1, Section 8.4.2, and Section 8.4.3, respectively. Guidance for the prophylaxis for TLS and the anticipated B-cell depletion and associated risk of infection are provided in Section 8.4.4 and

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Section 8.4.5, respectively. Upon occurrence of a toxicity, the investigator, with input from the sponsor, as needed, will assess the etiology of the toxicity.

Full emergency resuscitation facilities should be immediately available, and participants should always be under close supervision of the investigator.

8.4.1. Acute Allergic/Hypersensitivity Reactions

Emergency equipment and medication for the treatment of infusion reactions must be available for immediate use. All infusion reactions must be reported as AEs (as defined in Section 10.3.1) and graded using the grading scales as instructed in Section 10.3.4.

8.4.1.1. Interruption of the Intravenous Infusion

The infusion should be interrupted if any of the following AEs are observed:

- Sustained/severe cough
- Rigors/chills
- Rash, pruritus (itching)
- Urticaria (hives, welts, wheals)
- Diaphoresis (sweating)
- Hypotension
- Dyspnea (shortness of breath)
- Vomiting
- Flushing

The reaction(s) should be treated symptomatically, and the infusion may be restarted at 50% of the original rate.

If investigators feel there is a medical need for treatment or discontinuation of the infusion other than described above, they should use clinical judgment to provide the appropriate response according to typical clinical practice.

8.4.1.2. Termination of the Intravenous Infusion

The infusion of odronextamab (and potentially CHOP/CVP and rituximab) should be terminated and NOT restarted if any of the following AEs occur:

- Anaphylaxis*
- Laryngeal/pharyngeal edema
- Severe bronchospasm
- Chest pain
- Seizure
- Severe hypotension

- Other neurological symptoms (confusion, loss of consciousness, paresthesia, paralysis, etc.)
- Any other symptom or sign that, in the opinion of the investigator, warrants termination of the IV infusion

*Consider anaphylaxis if the following is observed (Sampson, 2006): acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips/tongue/uvula) AND AT LEAST ONE OF THE FOLLOWING:

- Respiratory compromise (eg, dyspnea, wheeze/bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
- Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

8.4.2. Infusion-Related Reactions (IRRs) and Cytokine Release Syndrome (CRS)

Given that acute toxicity (e.g., CRS, IRRs, acute allergic hypersensitivity) is most likely to occur with the first administration and less likely to recur with subsequent administrations, participants who experience such events with the first administration of odronextamab may be considered for continued treatment once the toxicity resolves to grade 1 or baseline (Table 15). IRRs and CRS are anticipated toxicities of odronextamab therapy. An acute IRR is defined as any AE that occurs less than 6 hours from the start of the odronextamab infusion or within 2 hours after completion of the odronextamab infusion (whichever is later) and is associated with typical signs and symptoms including but not limited to flushing, tachycardia, hypotension, dyspnea, bronchospasm, back pain, fever, urticaria, edema, nausea, and rashes. Cytokine release syndrome is a disorder characterized by fever, tachypnea, headache, tachycardia, hypotension, rash, and/or hypoxia; in this study it is defined as such an event that occurs 6 or more hours from the start of the odronextamab infusion or more than 2 hours after completion of the odronextamab infusion (whichever is later).

To mitigate the risk and reduce the severity of these events, premedication with dexamethasone prior to odronextamab, split dosing of odronextamab and close monitoring are required. Medications (including epinephrine for subcutaneous injection, corticosteroids, diphenhydramine hydrochloride for IV injection) and resuscitation equipment should be available for immediate use. In the event of IRR and/or CRS, management guidelines for odronextamab are provided in Table 17 and Table 18. For management guidelines for rituximab, please refer to the approved label.

Table 15: Dose Modification of Odronextamab for IRR

Toxicity[1]	Management	Re-challenge
Grade 4	Permanently discontinue odronextamab if IRR event is due to odronextamab. Administer supportive care aggressively – eg, antipyretics, antihistamines, and/or meperidine. Consider corticosteroids.	Do not re-challenge.

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Grade 3	Temporarily pause odronextamab. Administer supportive care – eg, antipyretics, antihistamines, and/or meperidine. Consider corticosteroids.	May resume treatment when clinical symptoms are resolved. If participant was at initial dose, re-initiate treatment at the initial dose and escalate as tolerated. If participant was at intermediate doses, re-initiate treatment at a dose that is no higher than the prior administered intermediate dose and escalate as tolerated. If participant was at the first weekly full dose, reduce to no more than 50% of the weekly full dose and escalate to weekly full dose as tolerated. Continue dosing if no recurrence of toxicity.
Grade 1 or 2	Temporarily pause odronextamab. Administer supportive care – eg, antipyretics, antihistamines, and/or meperidine. No dose modification required.	No dose modification required. May resume when clinical symptoms are at baseline.

[1]Toxicity is assessed by NCI-CTCAE v5.0 for infusion related reaction (IRR).

Provided subsequent administration is tolerated, participants who received a modified dose may have their dose increased per the assigned dose regimen (e.g., no higher than the full dose for the assigned dose regimen) based on the clinical judgment of the investigator in consultation with the sponsor.

In any of the above circumstances, the investigators should use their best clinical judgment as to whether the participant should receive continued treatment. Additionally, the investigator may choose to deliver a lower dose than recommended in Table 10, if it is deemed to be in the best interest of the participant after discussion with the sponsor. For premedication guidelines, see Section 8.2.

Cytokine release syndrome management guidelines, including clinical evaluation and monitoring, are detailed in Table 16, Table 17, and Table 18.

Table 16: CRS Toxicity Grading

CRS Parameter	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Fever[1]	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
			With	
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
			And/or[2]	
Hypoxia	None	Requiring low-flow nasal cannula[3] or blow-by	Requiring high-flow nasal cannula,[3] facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg CPAP, BiPAP, intubation and mechanical ventilation)

*Adapted from American Society for Transplantation and Cellular Therapy (ASTCT) Cytokine Release Syndrome Consensus Grading (Lee, 2019).
CPAP=continuous positive airway pressure, bilevel positive airway pressure, BiPAP=bilevel positive airway pressure.

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Organ toxicities associated with CRS may be graded according to CTCAE v4.03 in Part A and CTCAE v5.0 in Part B, but they do not influence CRS grading.

[1] Fever is defined as temperature ≥ 38°C not attributable to any other cause. In participants who have CRS then receive antipyretic or anti-cytokine therapy such as anti-IL-6 (e.g. tocilizumab) or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

[2] CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a participant with temperature of 39.5°C, hypotension requiring 1 vasopressor and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

[3] Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

Table 17: Management Guidance and Odronextamab Dosing in Setting of CRS

Event	Grade	Action with Odronextamab	Management Guide	Rechallenge
CRS*	1	Temporarily pause study drug	• Vigilant supportive care • Assess for infection • Treat febrile neutropenia if present, monitor fluid balance • Antipyretics/analgesics and IV fluids as needed • Monitor cardiac and other organ functions closely • Symptomatic management of organ toxicities • Monitor vital signs at least every hour ±30 minutes until resolution of clinical symptoms. Additional monitoring may be required as clinically indicated Treatment: **Refer to** Table 18	No dose modification required. May resume when clinical symptoms are resolved to baseline
CRS*	2	Temporarily pause study drug	• Vigilant supportive care • Assess for infection • Treat febrile neutropenia if present, monitor fluid balance • Antipyretics/analgesics and IV fluids as needed • Monitor cardiac and other organ functions closely • Symptomatic management of organ toxicities • Monitor vital signs at least every hour ±30 minutes until resolution of clinical symptoms. Additional monitoring may be required as clinically indicated Treatment: **Refer to** Table 18	No dose modification required. May resume when clinical symptoms are baseline

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Event	Grade	Action with Odronextamab	Management Guide	Rechallenge
	3	Temporarily pause study drug	• Vigilant supportive care as per grade 2 • Vasopressor support for fluid refractory hypotension and intensive care unit (ICU) care as needed • Supplemental oxygen as needed Treatment: **Refer to** Table 18	Repeat dose if it occurred with initial dose. For intermediate dose 1, intermediate dose 2, or full target dose, reduce by at least 50%. May resume when clinical symptoms are baseline
	4	Permanently discontinue	• Vigilant supportive care as per grade 2 • ICU care, hemodynamic monitoring, vasopressor support, ventilatory support as needed Treatment: **Refer to** Table 18	Not applicable

CRS=cytokine release syndrome; ICU=intensive care unit; IV=intravenous.
*Adapted from
(Lee, 2019) and (Neelapu, 2018)

Table 18: Guidelines for Administration of Anti-IL6 Receptor Therapy (e.g. Tocilizumab) and Corticosteroids in the Setting of CRS

CRS Grade	Administer anti-IL6 Therapy (eg tocilizumab*) in the following scenarios	Administer corticosteroid
Any grade CRS	• Earlier use of anti-IL6 (eg tocilizumab) is recommended for elderly participants (age > 65 years) or for participants with co-morbidities as per investigator's clinical judgement	• Refer to corresponding grade of CRS
Grade 1 CRS	• Participants with persistent [lasting >3 days] and refractory fever	• Dexamethasone 10 mg IV (or equivalent corticosteroid) every 24 hours
Grade 2 CRS	• Hypotension that is refractory to fluid boluses • Hypoxia • Left ventricular ejection fraction < 40% by echocardiogram • Creatinine > 2.5-fold higher than the most recent level prior to odronextamab infusion/injection • Activated partial thromboplastin time > 2x ULN • Clinically significant bleeding • Creatine kinase > 5x ULN for longer than 2 days	• Dexamethasone 10 mg IV (or equivalent corticosteroid) every 12 to 24 hours • If no improvement or rapid progression of CRS, increase dexamethasone to 10 to 20 mg IV (or equivalent corticosteroid) every 6 to 12 hours
Grade 3 CRS	• Any grade 3	• Dexamethasone 10 to 20 mg IV (or equivalent corticosteroid) every 6 to 12 hours

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CRS Grade	Administer anti-IL6 Therapy (eg tocilizumab*) in the following scenarios	Administer corticosteroid
Grade 4 CRS	• Any grade 4	• Dexamethasone 20 mg IV (or equivalent corticosteroid) every 6 hours

*** tocilizumab dose:** 8 mg/kg infused over 1 hour, dose not to exceed 800 mg. Repeat doses of tocilizumab may be administered as required according to the label (if no clinical improvement in the signs and symptoms of CRS occurs after the first dose, up to 3 additional doses may be administered. The interval between consecutive doses should be at least 8 hours)
Sites should ensure that two doses of an anti-IL6 therapy such as tocilizumab are available before any study drug is administered during step-up dosing of every patient.
Guidelines adapted from (Brudno, 2016) (Neelapu, 2018) (Maus, 2020)

8.4.3. Central Nervous System Toxicity (ICANS)

ICANS is a stereotypic disorder characterized by a pathologic process involving the central nervous system following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune-effector cells. Symptoms or signs can be progressive and may include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral edema. ICANS may have features that overlap with other encephalopathies although some symptoms such as expressive aphasia maybe more specific for ICANS (Lee, 2019).

Other neurological symptoms and/or signs may occur and possibly be attributable to immune-effector cell-engaging therapies. As isolated signs/symptoms, these are not considered ICANS, and are considered under other neurologic events. For example, headache or tremor with no decrease in Immune- Effector Cell-Associated Encephalopathy (ICE) score or no decreased level of consciousness, disorientation, or other stereotypic symptoms or signs of ICANS would not be considered ICANS.

Any neurologic symptoms including symptoms seen in cases of ICANS may also be observed in association with other pathological processes, including the examples listed below. Neurologic symptoms considered wholly explained by other processes like these would not be considered ICANS.

- Hepatic failure, severe hypertension, infection, or electrolyte or other laboratory abnormalities
- Adverse reactions to immunosuppressive therapies, cytotoxic drug therapies, or other concomitant medications
- Underlying disease processes, e.g. a pre-existing seizure disorder

The CARTOX-10-based grading tool for ICANS, termed the ICE score, is described in Table 19 . The ICE score should be used to grade all cases of ICANS in this trial.

Participants who experience ICANS grade ≥ 3 at any time on study treatment will be required to discontinue study drug permanently if the signs or symptoms are attributed wholly or primarily to odronextamab treatment. If odronextamab treatment is considered to be a possible contributor to the ICANS event but not its primary etiology, then study drug dosing must be interrupted until

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ICANS signs and symptoms resolve to grade 1 or baseline; at such a time, the study drug may be resumed at the discretion of the investigator after discussion with the medical monitor. Study drug must also be interrupted in participants who experience lower grade signs or symptoms consistent with ICANS toxicity, and study drug may be resumed after resolution of signs or symptoms to baseline following discussion and agreement by the investigator and the sponsor (Neelapu, 2018).

Participants should be evaluated on cycle 1 day 1 prior to infusion for assessment of baseline neurological and mental status. The following domains should be tested: orientation, naming, following commands writing, and attention (ICE-Tool) as shown in Table 19. ICANS grading should be according to the ASTCT consensus grading (Lee, 2019) as shown in Table 20. Guidelines for the management of neurotoxicity events in the setting with CRS and without CRS are described in Table 21.

Table 19: Immune-Effector Cell-Associated Encephalopathy (ICE) Assessment Tool for Determination of ICE Score

Orientation	Orientation to year, month, city, hospital: **4 points**
Naming	Ability to name 3 objects (e.g. point to clock, pen, button): **3 points**
Following Commands	Ability to follow simple commands (e.g. "show me 2 fingers" or "close your eyes and stick out your tongue"): **1 point**
Writing	Ability to write a standard sentence (e.g. "Our national bird is the bald eagle."): **1 point**
Attention	Ability to count backwards from 100 by 10: **1 point**
ICE Scoring	10: no impairment 7-9: grade 1 ICANS 3-6: grade 2 ICANS 0-2: grade 3 ICANS 0 due to patient unarousable and unable to perform ICE assessment: grade 4 ICANS

ICANS=Immune-effector cell-associated neurotoxicity syndrome; ICE=Immune Effector Cell-Associated Encephalopathy.
Based on Lee, 2019

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Table 20: Immune-Effector Cell-Associated Neurotoxicity Syndrome (ICANS) Consensus Grading for Adults

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7-9	3-6	0-2	0 (if patient is unarousable and unable to perform ICE)
Depressed level of consciousness†	Awakes spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse; stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or repetitive clinical or electrical seizures without return to baseline in between
Motor findings‡	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging§	Diffuse cerebral edema on neuroimaging decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.
N/A indicates not applicable.
*A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.
†Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).
†Tremors and myoclonus- associated immune-effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.
§Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.
Based on Lee, 2019.

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Table 21: Guidelines for Management of ICANS

For ICE assessment, please refer to the ICE tool in Table 19.
For ICANS consensus grading for adults, please refer to Table 20.

ICANS Grade	Action with study medication	Management		Re-challenge
		No concurrent CRS	If concurrent CRS	
Grade 1	Temporarily discontinue study treatment until resolution of ICANS	• Supportive care ○ Consider neurology consultation, including EEG and brain imaging, per investigator ○ Monitoring of neurologic symptoms per investigator ○ Consider seizure prophylaxis per investigator with non-sedating, antiseizure medicines (such as levetiracetam) • Consider dexamethasone	• Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg/dose)[d]	After resolution of symptoms
Grade 2[a]	Temporarily discontinue study treatment until resolution of ICANS	• Supportive care as per Grade 1 • 1 dose of dexamethasone 10 mg IV and reassess. Repeat every 6-12 hours as needed until resolution or baseline	• Anti-IL-6 therapy as per Grade 1 • Consider transferring participant to ICU if neurotoxicity associated with grade ≥2 CRS	After resolution of symptoms
Grade 3[a]	Discontinue study treatment permanently	• ICU care is recommended • Supportive care as per Grade 1 • Dexamethasone 10 mg IV every 6 hours or methylprednisolone, 1 mg/kg IV every 12 hours[b, c] • Consider repeat neuroimaging (CT or MRI) every 2-3 days if patient has persistent grade ≥3 neurotoxicity	• Anti-IL-6 therapy as per Grade 1	• Permanently discontinue treatment if symptoms occurred in the absence of alternative etiology* • **Alternative etiology for symptoms.** May resume treatment after the symptoms have resolved to Grade 1 or baseline

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ICANS Grade	Action with study medication	Management		Re-challenge
		No concurrent CRS	If concurrent CRS	
Grade 4[a]	Discontinue study treatment permanently	• ICU care, consider mechanical ventilation for airway protection • Supportive care as per Grade 1 • High-dose corticosteroids[b,c] • Consider repeat neuroimaging (CT or MRI) every 2-3 days if patient has persistent grade ≥3 neurotoxicity • Treat convulsive status epilepticus per institutional guidelines • If raised ICP/cerebral edema, follow standard of care measures to control intracranial pressure; consider neurosurgery consultation	• Anti-IL-6 therapy as per Grade 1	• Permanently discontinue treatment if symptoms occurred in the absence of alternative etiology* • **Alternative etiology for symptoms**. May resume treatment after the symptoms have resolved to Grade 1 or baseline

*CNS symptoms in the absence of alternative etiology
[a] Diagnostic lumbar puncture for grade 3-4 neurotoxicity, consider for grade 2
[b] Antifungal prophylaxis is strongly considered in participants receiving steroids for the treatment of CRS and/or neurotoxicity as per investigator
[c] For example, methylprednisolone IV 1000 mg/day (may consider twice a day) for 3 days, followed by rapid taper at 250 mg every 12 hours for 2 days, 125 mg every 12 hours for 2 days, and 60 mg every 12 hours for 2 days
[d] Repeat tocilizumab every 8 hours as needed if not responsive to IV fluids or increasing supplemental oxygen. Limit to maximum of 3 doses in a 24-hour period.
Adapted from (National Comprehensive Cancer Network (NCCN), 2021)

8.4.4. Tumor Lysis Syndrome

8.4.4.1. Recommendations for TLS Prophylaxis

For recommendations for TLS prophylaxis prior to rituximab infusion, please refer to the approved label.

All participants should have adequate fluid intake (approximately 2 to 3 L/day) oral or IV (if unable to take oral fluids) starting 1 to 2 days prior to the odronextamab infusion and continued for at least 24 hours after infusion until the participant tolerates the step-up dose of odronextamab administered as a single infusion or until the investigator determines that the participant is not at risk for TLS, whichever is later.

Participants considered at risk for TLS by the investigator should have the following additional measures taken for TLS prophylaxis:

- Such participants should receive prophylaxis with allopurinol (or other hypouricemic agent). Allopurinol should begin preferably 7 to 10 days prior to the first infusion of study drug but not less than 48 hours prior to the first administration. Participants who

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cannot tolerate allopurinol or another hypouricemic agent and who are at risk for TLS should be monitored closely and treated with rasburicase according to the prescribing information and pertinent institutional guidelines for TLS prophylaxis.

- In addition to oral hydration noted above, IV hydration (approximately 1.5 to 2 L) should be administered as permitted by the participant's hemodynamic status and according to the investigator's clinical judgment.
- If laboratory abnormalities that in the investigator's judgment indicate ongoing TLS are observed in this baseline laboratory assessment, the first dose of study treatment must be delayed until resolution of laboratory abnormalities. If needed, the participant should receive an extended period of TLS prophylaxis prior to the initiation of odronextamab dosing.
- Participant should continue the oral hypouricemic agent (if feasible) or rasburicase until the participant tolerates the step-up dose of odronextamab administered as a single injection through cycle 2 day 1 of study treatment or until the investigator determines that the participant is not at risk for TLS, whichever is later.

8.4.4.2. Required Monitoring for Tumor Lysis Syndrome

The TLS risk should be assessed by the investigator before each study drug administration until the participant has been determined to tolerate the step-up dose of odronextamab administered as a single infusion or until the investigator determines that the participant is not at risk for TLS, whichever is later. Pre-dose laboratory results must be reviewed prior to administration of odronextamab. Participants considered by the investigator to be at risk for TLS must be closely monitored.

8.4.4.3. Dose Modification of Odronextamab for Participants who Experience Tumor Lysis Syndrome

If a participant receiving study treatment develops one or more laboratory or clinical abnormalities that are judged by the investigator to indicate TLS, study drug administration must be suspended immediately until all laboratory abnormalities and clinical signs/symptoms of TLS have resolved.

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Table 22: Management Guidance and Study Drug Dosing in Setting of TLS

Study Drug Administration	Outcome of TLS[1]	Action with odronextamab	Rechallenge[2]	TLS Management Guidance
TLS occurs with initial dose	Any grade of TLS that does not resolve within 14 days despite appropriate management	Permanently discontinue	Not applicable	A participant who has laboratory or clinical abnormalities indicative of TLS should be monitored closely. IV fluids should be initiated (approximately 150 to 200 mL/h). A rapidly rising serum potassium level is a medical emergency and should be managed according to standard clinical practice or local institutional guidelines. Other electrolyte abnormalities including hypocalcemia, hyperphosphatemia, and hyperuricemia should be managed according to standard clinical practice or local institutional guidelines. Monitor for symptoms or signs of TLS. If any clinical features are observed, recheck potassium, phosphorus, uric acid, calcium, and creatinine with an expedited assessment. Once the diagnosis of TLS is determined, intensive monitoring and multi-disciplinary management will be according to standard clinical practice or local institutional guidelines. Strongly recommend consultation with the nephrology service to ensure that emergency dialysis is available. Ensure that telemetry is available for monitoring.
	Any grade of TLS that resolves	Temporary pause	Upon resolution of TLS, resume treatment with: Treat with only the initial split dose (0.2 mg) and monitor for TLS. If no recurrence of TLS, then increase next dose to 0.7 mg administered as split doses (0.2/0.5 mg) **at least 2 days** apart but not more than 3 days apart. If no recurrence of TLS, dose may be escalated to a split intermediate dose 1 **at least 2 days** apart but not more than 3 days apart. If no recurrence of TLS with intermediate dose 1, escalate to next higher dose specified in protocol (ie, intermediate dose 2) as split dose **at least 2 days** apart but not more than 3 days apart.	
TLS occurs with intermediate doses and/or subsequent doses	Any grade of TLS that does not resolve within 14 days despite appropriate management	Permanently discontinue	Not applicable	
	Any grade of TLS that resolves	Temporary pause	Upon resolution of TLS, reduce previously received dose by 50% and monitor for TLS. If no recurrence of TLS, then escalate to the dose where TLS was last noted. This dose needs to be administered as a split dose **at least 2 days** apart but not more than 3 days apart.	

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Study Drug Administration	Outcome of TLS[1]	Action with odronextamab	Rechallenge[2]	TLS Management Guidance
			If no recurrence of TLS, dose may escalate to next higher dose specified in protocol as split dose **at least 2 days** apart but not more than 3 days apart.	

[1] Resolution of TLS is defined as no clinical or laboratory abnormalities suggestive of TLS in the investigator's judgment.

[2] If 2 consecutive TLS events occur, discuss the plan of study treatment with the Regeneron medical monitor. The goal is to idle the patient at a dose just below that which produces TLS until there is enough debulking of the tumor to allow dose escalation.

8.4.5. B-Cell Depletion and Infection Prophylaxis

Treatment with odronextamab or rituximab is expected to result in pronounced and prolonged B-cell depletion resulting in increased risk of infection. Participants with known active bacterial, viral, fungal, mycobacterial, or other infections or any major episode of infection requiring hospitalization or treatment with IV anti-infectives within 2 weeks prior to first administration of odronextamab or rituximab are excluded from the trial.

Participants with infections other than tuberculosis or opportunistic infection may resume treatment with study drug only if the infection is adequately controlled. In the case of HBV reactivation, the participant must have an undetectable viral load by HBV DNA-PCR (or equivalent method) on anti-viral therapy for HBV.

Cytomegalovirus infections and infections of grade 3 severity and above should be reported as adverse events of special interest (AESIs).

Recommendations for prophylaxis to decrease the risk of infections (for odronextamab and rituximab):

1. Participants should have evaluation of IgG levels at baseline as well as periodic monitoring throughout the study. In participants with severe hypogammaglobulinaemia (<400 mg/dL) or in participants with recurrent episodes of infection with immunoglobulin levels between 400 to 600 mg/dL, supplementation with intravenous immunoglobulin (IVIG) is recommended in accordance with the local institutional guidelines.
2. Participants with prior HBV infection should have periodic monitoring to detect hepatitis B reactivation using HBV DNA-PCR (or equivalent method) according to the local institutional guidelines. For participants with positive hepatitis B surface antigen, Hepatitis B core antibody (HBcAB), and/or measurable viral load, appropriate antiviral agent for HBV is recommended.
3. Prophylaxis for *Pneumocystis jirovecii* pneumonia (PJP) must be given to all participants during the treatment. The choice of the prophylactic agent and the duration of prophylaxis is determined by the treating physician.

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4. Participants should have periodic CMV monitoring done by PCR assay on peripheral blood samples (schedule in Section 9.1). If CMV DNA levels are detected at any time, consider antiviral treatment for CMV as deemed appropriate by the investigator and contact the medical monitor for additional recommendations; continue weekly monitoring by PCR until viral load decreases and then every 2 weeks (±1 week) until 2 consecutive undetectable results.
5. Appropriate antiviral prophylaxis for participants with prior Herpes Simplex Virus (HSV) or CMV infections is recommended. The choice of the prophylactic agent and the duration of prophylaxis is in accordance with the local institutional guidelines.
6. Standard measures of prophylaxis for infections should be considered in accordance with the local institutional standards as well as the National Comprehensive Cancer Network (National Comprehensive Cancer Network [NCCN], 2019), American Society of Clinical Oncology (ASCO) (Taplitz, 2018), or European Society for Medical Oncology (ESMO) (Klastersky, 2016) guidelines are recommended.

8.5. Method of Treatment Assignment

Approximately 446 participants will be randomized in Part 2 at a 1:1 ratio to receive either odronextamab or rituximab according to a central randomization scheme provided by an interactive voice response system (IVRS)/interactive web response system (IWRS) to the designated study pharmacist (or qualified designee). Randomization will be stratified as described in Section 6.1.1.3.

8.6. Blinding

This is an open label study. Sponsor's clinical study team members will remain blinded to treatment assigned at randomization but will have knowledge of treatment received by study participants for the purposes of data monitoring and cleaning. The primary endpoint of the study is based on response determination by independent central efficacy reviewers who will be blinded to both treatment assignment and treatment received.

8.7. Treatment Logistics and Accountability

8.7.1. Packaging, Labeling, and Storage for Odronextamab

Open-label study drug will display the product lot number on the label.

Study drug will be stored at the site at a temperature of 2°C to 8°C; storage instructions will be provided in the pharmacy manual.

8.7.2. Supply and Disposition of Treatments for Odronextamab

Study drug will be shipped at a temperature of 2°C to 8°C to the investigator or designee at regular intervals or as needed during the study. At specified timepoints during the study (eg, interim site monitoring visits), at the site close-out visit, and following drug reconciliation and documentation by the site monitor, all opened and unopened study drug will be destroyed or returned to the sponsor or designee.

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8.7.3. Treatment Accountability

All drug accountability records must be kept current.

The investigator must be able to account for all opened and unopened study drug. These records should contain the dates, quantity, and study medication:

- dispensed to each participant,
- returned from each participant (if applicable), and
- disposed of at the site or returned to the sponsor or designee.

All accountability records must be made available for inspection by the sponsor and regulatory agency inspectors; photocopies must be provided to the sponsor at the conclusion of the study.

8.7.4. Treatment Compliance

All drug compliance records must be kept current and made available for inspection by the sponsor and regulatory agency inspectors.

8.7.5. Handling of Drugs Used in R1979-HM-2298

When the DUICT will be provided by the sponsor, the drugs used in the clinical trial will be managed in accordance with the latest scientific findings (Section 3.2.2) in addition to a manual of drugs used in the clinical trial that will be separately prepared by the sponsor.

When the DUICT will be provided by each site, the drugs used in the clinical trial will be managed in accordance with the procedures of each site.

8.8. Concomitant Medications and Procedures

Transient elevation of cytokines may suppress CYP450 enzyme activities. The highest risk is during cycle 1 in participants who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index.

For these participants, monitoring of the effect (eg, warfarin) or drug concentration (eg, cyclosporine or theophylline) is recommended, especially until conclusion of step-up dosing period of odronextamab and DLT period after starting treatment with odronextamab.

Any treatment administered from the time consent is obtained until 90 days following the last dose of study drug regimen or start of non-protocol anti-lymphoma therapy, whichever occurs first, will be considered concomitant medication. This includes medications that were started before the study and are ongoing during the study.

All concomitant medications and concomitant procedures should be recorded on the appropriate electronic case report form (eCRF).

8.8.1. Prohibited Medications and Procedures

While participating in this study, a participant may not receive any of the following during the period defined for concomitant treatments and procedures in Section 8.8 unless otherwise specified below:

- Cytotoxic chemotherapy (other than those specified in this protocol)

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- Immunotherapy (other than those specified in this protocol)
- Hormone therapy (other than contraceptives, hormone-replacement therapy, or megestrol acetate)
- Corticosteroids: ongoing systemic treatment of more than 10 mg per day of prednisone/prednisolone or anti-inflammatory equivalent except as specified in the protocol or for treatment of an AE
- Any therapies intended for the treatment of lymphoma, whether authorized by the FDA, EMA, or other regulatory agency, or experimental in nature
- Radiotherapy (exceptions described in Section 8.8.2)
- Live vaccination: Participants should not receive live vaccination within 28 days of the first administration of odronextamab. In addition, no live vaccination should be administered during the odronextamab treatment period until at least 12 weeks after the last dose of odronextamab or until recovery of B lymphocytes to normal ranges following the last treatment, whichever is later. The treating physician should take into consideration the recovery of B-lymphocyte number and function according to the local institutional guidelines for vaccination of immunocompromised participants.

Participants who require the use of any of these agents or procedures described above will be discontinued from study treatment.

8.8.2. Permitted Medications and Procedures

The following medications and procedures will be permitted in the following circumstances:

- Any medication required to treat an AE, including systemic corticosteroids
- Corticosteroid therapy for participants requiring physiologic replacement therapy or requiring a brief course for prophylaxis (eg, for contrast dye allergy) or for treatment of nonautoimmune conditions (eg, delayed-type hypersensitivity reaction caused by contact allergen)
- **Treatment and prophylaxis of neutropenia.** G-CSF, platelet, or red blood cell transfusions are permitted for participants who require hematopoietic support. Prophylactic use of G-CSF is allowed per institutional standards or guidelines from the ASCO or European Organisation for Research and Treatment of Cancer. A participant may not have received G-CSF within 2 days prior to first dose of odronextamab or platelet transfusion within 7 days prior to first dose of odronextamab in order to meet the ANC and platelet eligibility criteria, respectively.
- Local radiation or surgery for palliative/symptom control only, in the absence of disease progression, is permitted
- Any other medication, which is considered necessary for the participant's welfare and which is not expected to interfere with the evaluation of the study drug, may be administered at the discretion of the investigator.

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9. STUDY SCHEDULE OF EVENTS AND PROCEDURES

9.1. Schedule of Events

In light of the public health emergency related to COVID-19, the continuity of clinical study conduct and oversight may require implementation of temporary or alternative mechanisms. Examples of such mechanisms may include but are not limited to any of the following: phone contact, virtual visits, telemedicine visits, online meetings, non-invasive remote monitoring devices, use of local clinic or laboratory locations, and home visits by skilled staff. Additionally, no waivers to deviate from protocol enrollment criteria due to COVID-19 will be granted. All temporary mechanisms utilized and deviations from planned study procedures are to be documented as being related to COVID-19 and will remain in effect only for the duration of the public health emergency.

Study assessments and procedures are presented by study period and visit in Table 23 , (odronextamab), Table 24 (odronextamab follow-up), Table 25 (rituximab-CHOP/CVP), and Table 26 (rituximab + bendamustine).

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Table 23: Schedule of Events for Odronextamab Monotherapy Arm

Study Procedure[1]	**Screening**	**Induction Treatment Period**																						**Maintenance (M) Treatment Period[23]**
Cycle / Maintenance	**Screening[1]**	**Cycle 1 (step-up dosing)**						**Cycle 2**			**Cycle 3**			**Cycle 4**			**Cycle 5**			**Cycle 6**			**M1 to M12**
Visit Day	**D-28 to -1**	**D 1**	**D 2**	**D 8**	**D 9**	**D 15**	**D 16**	**D 1**	**D 8**	**D 15**	**D 1**	**D 8**	**D 15**	**D 1**	**D 8**	**D 15**	**D 1**	**D 8**	**D 15**	**D 1**	**D 8**	**D 15**	**D1 (Q8W)**
Visit Window (days)		**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**
Screening/Baseline																								
Informed consent	X																							
Genomics informed consent[3]	X																							
Demographics	X																							
Inclusion/exclusion criteria	X																							
Medical/oncologic history	X																							
Complete physical exam[4]	X																							
Brain MRI or CT	X																							
Safety																								
Vital signs[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X	X	
Height	X																							
Weight	X	X						X			X			X				X		X			X	
Limited physical exam		X						X			X			X				X		X			X	
Lymphatic exam		X						X			X			X				X		X			X	
Neurological examination[24]		X																						
ECOG performance status	X	X		X		X		X			X			X				X		X		X	X	
Assess for B symptoms	X	X		X		X		X			X			X				X		X		X	X	
Adverse events[6]		Ongoing																						
Concomitant medications/ procedures[7]		Ongoing																						

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Study Procedure[1]	**Screening**	**Induction Treatment Period**																					**Maintenance (M) Treatment Period[23]**
Cycle / Maintenance	**Screening[1]**	**Cycle 1 (step-up dosing)**						**Cycle 2**			**Cycle 3**			**Cycle 4**			**Cycle 5**			**Cycle 6**			**M1 to M12**
Visit Day	**D-28 to -1**	**D 1**	**D 2**	**D 8**	**D 9**	**D 15**	**D 16**	**D 1**	**D 8**	**D 15**	**D 1**	**D 8**	**D 15**	**D 1**	**D 8**	**D 15**	**D 1**	**D 8**	**D 15**	**D 1**	**D 8**	**D 15**	**D1 (Q8W)**
Cardiac ejection fraction (Echo or MUGA)	X	Only if clinically indicated																					
12-lead ECG[21]	X																	X					
Treatment																							
Monitoring observation[8]		X	X	X	X	X	X	X															X
Odronextamab		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X	X[24]
Laboratory Tests																							
Hematology	X	X						X			X			X				X		X			X
Blood chemistry	X	X						X			X			X				X		X			X
Serum IgG	X																	X					X
PT (INR)/PTT or aPTT[9]	X																	X					
CMV PCR[11]	X																	X					
HIV, HCV, HBV[10]	X																						
Serum beta-2 microglobulin	X																						
Urinalysis	X																						
Pregnancy test[12]	X	X						X			X			X				X				X	X
Drug Concentration and Immunogenicity Assessments																							
Drug concentration (PK) samples		Refer to Table 27																					
Immunogenicity (ADA) samples		Refer to Table 27																					
Tumor Assessments/ Efficacy[13]																							
CT or MRI[14]	X	W12 (± 14 days), W24 (±14 days), W36 (± 14 days), W48 (± 14 days), W72 (± 14 days), W96 (± 14 days), and W120 (± 14 days) followed by a clinical 90 day follow-up visit (±14 days), Q12W (± 14 days) for first 3 clinical Q12W follow-up visits, and Q24W (±14 days) thereafter, until progression, start of non-protocol anti-lymphoma therapy or at any time when disease progression is suspected.																					
FDG PET-CT[15]	X	If negative at screening, there is no need to repeat it. If positive at screening, FDG-PET is required in all the timepoints corresponding to CT or MRI assessments (see above).																					
BMA/BMBx[16]	X	To confirm CR (if positive at screening) or PD and per discretion of investigator																					

Study Procedure[1]	**Screening**	**Induction Treatment Period**																					**Maintenance (M) Treatment Period[23]**
Cycle / Maintenance	**Screening[1]**	**Cycle 1 (step-up dosing)**						**Cycle 2**			**Cycle 3**			**Cycle 4**			**Cycle 5**			**Cycle 6**			**M1 to M12**
Visit Day	**D-28 to -1**	**D 1**	**D 2**	**D 8**	**D 9**	**D 15**	**D 16**	**D 1**	**D 8**	**D 15**	**D 1**	**D 8**	**D 15**	**D 1**	**D 8**	**D 15**	**D 1**	**D 8**	**D 15**	**D 1**	**D 8**	**D 15**	**D1 (Q8W)**
Lymph node/tumor biopsy[17]	X	X (If Progressive Disease)																					
Biomarker Sampling[20]																							
Cytokine profiling (serum)		See detailed Table 27																					
Peripheral immunophenotyping		See detailed Table 27																					
ctDNA sample		See detailed Table 27																					
Blood collection - genomic DNA (optional)[18]		X																					
Patient-reported Outcome Assessment[19]																							
EORTC-QLQ-C30		X		X		X		X			X			X				X		X			X
EQ-5D-5L		X		X		X		X			X			X				X		X			X
FACT-LymS		X		X		X		X			X			X				X		X			X
PGIS		X		X		X		X			X			X				X		X			X
PGIC				X		X		X			X			X				X		X			X
FACT-G GP5 item				X		X		X			X			X				X		X			X

ADA=antidrug antibodies; aPTT=Activated partial thromboplastin time; BMA=Bone marrow aspiration; BMBx=Bone marrow biopsy; CHOP=Cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone; CT=Computed tomography; ctDNA=circulating tumor DNA; CVP=cyclophosphamide, vincristine, and prednisone/prednisolone; D=Day; DNA=Deoxyribonucleic acid; ECG=Electrocardiogram; Echo=Echocardiogram; ECOG=Eastern Cooperative Oncology Group; EORTC-QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; EQ-5D-5L=EuroQoL-5 Dimension-5 Level Scale; FACT-LymS=Function Assessment of Chronic Illness Therapy General-Lymphoma Lymphoma subscale;FDG-PET = 18F-fluorodeoxyglucose-positron emission tomography, HBV=Hepatitis B virus; HCV=Hepatitis C virus; HIV=Human immunodeficiency virus; IgG=Immunoglobulin G; INR=International normalized ratio; IV=Intravenous; max=Maximum; MRI=Magnetic resonance imaging; MUGA=Multi-gated acquisition scan; PET-CT=Positron emission tomography-computed tomography; PGIS=Patient Global Impression of Severity; PGIC=Patient Global Impression of Change; PO=By mouth; PT=Prothrombin time; PTT=Partial thromboplastin time; Q4W=Every 4 weeks; Q12W=Every 12 weeks; W=Week

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Table 24: Schedule of Events for Odronextamab Arm – Follow-Up Period

Study Procedure[1]	**Follow-Up[2]**		
Cycle / Maintenance	**Clinical Follow-Up**	**Clinical Q12W**	**Survival**
	90 Days Post Last Dose	**Follow-up**	**Follow-up**
Visit Day	**D1**	**D1 (Q12W)**	**D1 (Q12W)**
Visit Window (days)	**±7**	**±7**	**±7**
Safety			
Vital signs[5]	X	X	
Height			
Weight	X	X	
Limited physical exam	X	X	
Lymphatic exam	X	X	
ECOG performance status	X	X	
Assess for B symptoms	X	X	
Adverse events[6]	Ongoing	Only related SAEs	
Concomitant medications/ procedures[7]	Ongoing	Only for related SAEs	
Laboratory Tests			
Hematology	X	X	
Blood chemistry	X		
Serum IgG	X	X	
PT (INR)/PTT or aPTT[9]			
HIV, HCV, HBV[10]			
Urinalysis			
Pregnancy test[12]	X		
Drug Concentration and Immunogenicity Assessments			
Drug concentration (PK) samples	Refer to Table 27		

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Study Procedure[1]	**Follow-Up[2]**		
Cycle / Maintenance	**Clinical Follow-Up**	**Clinical Q12W**	**Survival**
	90 Days Post Last Dose	**Follow-up**	**Follow-up**
Visit Day	**D1**	**D1 (Q12W)**	**D1 (Q12W)**
Visit Window (days)	**±7**	**±7**	**±7**
Immunogenicity (ADA) samples	Refer to Table 27		
Tumor Assessments/ Efficacy[13]			
CT or MRI[14]	X	X[2c]	
PET-CT[15]		X[2c]	
BMA/BMBx[16]		X[2c]	
Lymph node/tumor biopsy[17]	X (If Progressive Disease)		
Biomarker Sampling[20]			
Peripheral immunophenotyping	Refer to Table 27		
ctDNA Sample	Refer to Table 27		
Patient-reported Outcome Assessment[19]			
EORTC-QLQ-C30	X	X	
EQ-5D-5L	X	X	
FACT-LymS	X	X	
PGIS	X	X	
PGIC	X	X	
Survival			

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Study Procedure[1]	**Follow-Up[2]**		
Cycle / Maintenance	**Clinical Follow-Up**	**Clinical Q12W**	**Survival**
	90 Days Post Last Dose	**Follow-up**	**Follow-up**
Visit Day	**D1**	**D1 (Q12W)**	**D1 (Q12W)**
Visit Window (days)	**±7**	**±7**	**±7**
Survival monitoring (can be done via phone)			X

ADA=antidrug antibodies; aPTT=Activated partial thromboplastin time; BMA=Bone marrow aspiration; BMBx=Bone marrow biopsy; CHOP=Cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone; CT=Computed tomography; ctDNA=circulating tumor DNA; CVP=cyclophosphamide, vincristine, and prednisone/prednisolone; D=Day; DNA=Deoxyribonucleic acid; ECG=Electrocardiogram; Echo=Echocardiogram; ECOG=Eastern Cooperative Oncology Group; EORTC-QLQC-30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; EQ-5D-5L=EuroQoL-5 Dimension-5 Level Scale; FACT-LymS=Function Assessment of Chronic Illness Therapy General-Lymphoma Lymphoma subscale; HBV=Hepatitis B virus; HCV=Hepatitis C virus; HIV=Human immunodeficiency virus; Ig=Immunoglobulin; INR=International normalized ratio; IV=Intravenous; max=Maximum; MRI=Magnetic resonance imaging; MUGA=Multi-gated acquisition scan; PET-CT=Positron emission tomography-computed tomography; PGIS=Patient Global Impression of Severity; PGIC=Patient Global Impression of Change; PO=By mouth; PT=Prothrombin time; PTT=Partial thromboplastin time; Q4W=Every 4 weeks; Q12W=Every 12 weeks; W=Week

Table 25: Schedule of Events for Rituximab-CHOP/CVP Arm

Study Procedure	**Screening**	**Induction Treatment Period**						**Maintenance (M) Treatment Period[23]**	**Follow-up[2]**		
Cycle / Maintenance	**Screening[1]**	**Cycle 1**	**Cycle 2**	**Cycle 3**	**Cycle 4**	**Cycle 5**	**Cycle 6**	**M1 to M12**	**Clinical Follow-up** **90 Days Post Last Dose**	**Clinical Q12W Follow-up**	**Survival Follow-up**
Visit Day	**D-28 to -1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1 (Q8W)**	**D1**	**D1 (Q12W)**	**D1 (Q12W)**
Visit Window		**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±7 days**	**±7 days**	**±7 days**
Screening/Baseline											
Informed consent	X										

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Study Procedure	**Screening**	**Induction Treatment Period**						**Maintenance (M) Treatment Period[23]**	**Follow-up[2]**		
Cycle / Maintenance	**Screening[1]**	**Cycle 1**	**Cycle 2**	**Cycle 3**	**Cycle 4**	**Cycle 5**	**Cycle 6**	**M1 to M12**	**Clinical Follow-up 90 Days Post Last Dose**	**Clinical Q12W Follow-up**	**Survival Follow-up**
Visit Day	**D-28 to -1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1 (Q8W)**	**D1**	**D1 (Q12W)**	**D1 (Q12W)**
Visit Window		**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±7 days**	**±7 days**	**±7 days**
Genomics informed consent[3]	X										
Demographics	X										
Inclusion/exclusion criteria	X										
Medical/oncologic history	X										
Complete physical exam[4]	X										
Brain MRI or CT	X										
Safety											
Vital signs[5]	X	X	X	X	X	X	X	X	X	X	
Height	X										
Weight	X	X	X	X	X	X	X		X	X	
Limited physical exam		X	X	X	X	X	X		X	X	
Lymphatic exam		X	X	X	X	X	X		X	X	
ECOG performance status	X	X	X	X	X	X	X		X	X	
Assess for B symptoms	X	X	X	X	X	X	X		X	X	
Adverse events[6]		Ongoing								Only related SAEs	

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Study Procedure	**Screening**	**Induction Treatment Period**						**Maintenance (M) Treatment Period[23]**	**Follow-up[2]**		
Cycle / Maintenance	**Screening[1]**	**Cycle 1**	**Cycle 2**	**Cycle 3**	**Cycle 4**	**Cycle 5**	**Cycle 6**	**M1 to M12**	**Clinical Follow-up** **90 Days Post Last Dose**	**Clinical Q12W Follow-up**	**Survival Follow-up**
Visit Day	**D-28 to -1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1 (Q8W)**	**D1**	**D1 (Q12W)**	**D1 (Q12W)**
Visit Window		**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±7 days**	**±7 days**	**±7 days**
Concomitant medications/procedures[7]		Ongoing								Only for related SAEs	
Cardiac ejection fraction (Echo or MUGA)	X										
12-lead ECG[21]	X					X					
Treatment (21-day Cycle)[22]											
Rituximab (R-CHOP/R-CVP arm)		X	X	X	X	X	X	X[24]			
Cyclophosphamide 750 mg/m^2 IV		X	X	X	X	X	X				
Doxorubicin 50 mg/m^2 IV		X	X	X	X	X	X				
Vincristine 1.4 mg/m^2 IV (max 2 mg)		X	X	X	X	X	X				
Prednisone/prednisolone 100 mg PO		X (D1 to D5)	X (D1 to D5)	X (D1 to D5)	X (D1 to D5)	X (D1 to D5)	X (D1 to D5)				
Laboratory Tests											
Hematology	X	X	X	X	X	X	X	X	X	X	
Blood chemistry	X	X	X	X	X	X	X	X	X	X	

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Study Procedure	**Screening**	**Induction Treatment Period**						**Maintenance (M) Treatment Period[23]**	**Follow-up[2]**		
Cycle / Maintenance	**Screening[1]**	**Cycle 1**	**Cycle 2**	**Cycle 3**	**Cycle 4**	**Cycle 5**	**Cycle 6**	**M1 to M12**	**Clinical Follow-up 90 Days Post Last Dose**	**Clinical Q12W Follow-up**	**Survival Follow-up**
Visit Day	**D-28 to -1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1 (Q8W)**	**D1**	**D1 (Q12W)**	**D1 (Q12W)**
Visit Window		**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±7 days**	**±7 days**	**±7 days**
Serum IgG immunoglobulin	X					X			X	X	
PT (INR)/PTT or aPTT[9]	X					X					
CMV PCR[11]	X					X					
HIV, HCV, HBV[10]	X										
Serum beta 2 microglobulin	X										
Urinalysis	X										
Pregnancy test[12]	X	X	X	X	X	X	X	X	X		
Tumor Assessments / Efficacy[13]											
CT or MRI[14]	X	W12 (± 14 days), W24 (±14 days), W36 (± 14 days), W48 (± 14 days), W72 (± 14 days), W96 (± 14 days) and W120 (± 14 days) followed by a clinical 90 day follow-up visit (±14 days), Q12W (± 14 days) at first 3 clinical Q12W follow-up visits and Q24W (±14 days) thereafter, until progression, start of non-protocol anti-lymphoma therapy or at any time when disease progression is suspected.								X[2c]	
FDG-PET-CT[15]	X	If positive at screening, FDG-PET is required in all the timepoints corresponding to CT or MRI assessments (See above).								X[2c]	
BMA/BMBx[16]	X	To confirm CR (if positive as screening) or PD and per as per discretion of investigator.								X[2c]	
Lymph node/tumor biopsy[17]	X	X (If Progressive Disease)									

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Study Procedure	**Screening**	**Induction Treatment Period**						**Maintenance (M) Treatment Period[23]**	**Follow-up[2]**		
Cycle / Maintenance	**Screening[1]**	**Cycle 1**	**Cycle 2**	**Cycle 3**	**Cycle 4**	**Cycle 5**	**Cycle 6**	**M1 to M12**	**Clinical Follow-up 90 Days Post Last Dose**	**Clinical Q12W Follow-up**	**Survival Follow-up**
Visit Day	**D-28 to -1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1 (Q8W)**	**D1**	**D1 (Q12W)**	**D1 (Q12W)**
Visit Window		**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±7 days**	**±7 days**	**±7 days**
Biomarker Sampling[20]											
Cytokine profiling (serum)		See detailed Table 27									
Peripheral immunophenotyping		See detailed Table 27									
ctDNA sample		See detailed Table 27									
Blood collection - genomic DNA (optional)[18]		X									
Patient-reported Outcome Assessment[19]											
EORTC-QLQ-C30		X	X	X	X	X	X	X	X	X	
EQ-5D-5L		X	X	X	X	X	X	X	X	X	
FACT-LymS		X	X	X	X	X	X	X	X	X	
PGIS		X	X	X	X	X	X	X	X	X	
PGIC			X	X	X	X	X	X	X	X	
GP5 (from FACT-G Questionnaire)			X	X	X	X	X	X			

Study Procedure	**Screening**	**Induction Treatment Period**						**Maintenance (M) Treatment Period[23]**	**Follow-up[2]**		
Cycle / Maintenance	**Screening[1]**	**Cycle 1**	**Cycle 2**	**Cycle 3**	**Cycle 4**	**Cycle 5**	**Cycle 6**	**M1 to M12**	**Clinical Follow-up 90 Days Post Last Dose**	**Clinical Q12W Follow-up**	**Survival Follow-up**
Visit Day	**D-28 to -1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1 (Q8W)**	**D1**	**D1 (Q12W)**	**D1 (Q12W)**
Visit Window		**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±7 days**	**±7 days**	**±7 days**
Survival											
Survival monitoring (can be done via phone)											X

aPTT=Activated partial thromboplastin time; BMA=Bone marrow aspiration; BMBx=Bone marrow biopsy; CHOP=Cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone; CT=Computed tomography; ctDNA=circulating tumor DNA; CVP=cyclophosphamide, vincristine, and prednisone/prednisolone; D=Day; DNA=Deoxyribonucleic acid; ECG=Electrocardiogram; Echo=Echocardiogram; ECOG=Eastern Cooperative Oncology Group; EORTC-QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; EQ-5D-5L=EuroQoL-5 Dimension-5 Level Scale; FACT-Lym=Function Assessment of Chronic Illness Therapy - Lymphoma subscale; FDG-PET=18F-fluorodeoxyglucose-positron emission tomography HBV=Hepatitis B virus; HCV=Hepatitis C virus; HIV=Human immunodeficiency virus; Ig=Immunoglobulin; INR=International normalized ratio; IV=Intravenous; max=Maximum; MRI=Magnetic resonance imaging; MUGA=Multi-gated acquisition scan; PET-CT=Positron emission tomography-computed tomography; PGIS=Patient Global Impression of Severity; PGIC=Patient Global Impression of Change; PO=By mouth; PT=Prothrombin time; PTT=Partial thromboplastin time; Q4W=Every 4 weeks; Q12W=Every 12 weeks; W=Week

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Table 26: Schedule of Events for Rituximab + Bendamustine

Study Procedure	**Screening**	**Induction Treatment Period**												**Maintenance (M) Treatment Period[23]**	**Follow-up[2]**		
Cycle / Maintenance	**Screening[1]**	**Cycle 1**		**Cycle 2**		**Cycle 3**		**Cycle 4**		**Cycle 5**		**Cycle 6**		**M1 to M12**	**Clinical Follow-up**	**Clinical Q12W Follow-up**	**Survival Follow-up**
															90 Days Post Last Dose		
Visit Day	**D-28 to -1**	**D1**	**D2**	**D1**	**D2**	**D1**	**D2**	**D1**	**D2**	**D1**	**D2**	**D1**	**D2**	**D1 (Q8W)**	**D1**	**D1 (Q12W)**	**D1 (Q12W)**
Visit Window		**±2 days**		**±2 days**		**±2 days**		**±2 days**		**±2 days**		**±2 days**		**±2 days**	**±7 days**	**±7 days**	**±7 days**
Screening/Baseline																	
Informed consent	X																
Genomics informed consent[3]	X																
Demographics	X																
Inclusion/exclusion criteria	X																
Medical/oncologic history	X																
Complete physical exam[4]	X																
Brain MRI or CT	X																
Safety																	
Vital signs[5]	X	X		X		X		X		X		X		X	X	X	
Height	X																
Weight	X	X		X		X		X		X		X			X	X	
Limited physical exam		X		X		X		X		X		X			X	X	
Lymphatic exam		X		X		X		X		X		X			X	X	

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Study Procedure	**Screening**	**Induction Treatment Period**												**Maintenance (M) Treatment Period[23]**	**Follow-up[2]**		
Cycle / Maintenance	**Screening[1]**	**Cycle 1**		**Cycle 2**		**Cycle 3**		**Cycle 4**		**Cycle 5**		**Cycle 6**		**M1 to M12**	**Clinical Follow-up** **90 Days Post Last Dose**	**Clinical Q12W Follow-up**	**Survival Follow-up**
Visit Day	**D-28 to -1**	**D1**	**D2**	**D1**	**D2**	**D1**	**D2**	**D1**	**D2**	**D1**	**D2**	**D1**	**D2**	**D1 (Q8W)**	**D1**	**D1 (Q12W)**	**D1 (Q12W)**
Visit Window		**±2 days**		**±2 days**		**±2 days**		**±2 days**		**±2 days**		**±2 days**		**±2 days**	**±7 days**	**±7 days**	**±7 days**
ECOG performance status	X	X		X		X		X		X		X			X	X	
Assess for B symptoms	X	X		X		X		X		X		X			X	X	
Adverse events[6]		Ongoing														Only related SAEs	
Concomitant medications/procedures[7]		Ongoing														Only for related SAEs	
Cardiac ejection fraction (Echo or MUGA)	X																
12-lead ECG[21]	X									X							
Treatment (28 Day Cycle)[22]																	
Bendamustine 90 mg/m^2		X	X	X	X	X	X	X	X	X	X	X	X				
Rituximab 375 mg/m^2 IV		X		X		X		X		X		X		X[24]			
Laboratory Tests																	
Hematology	X	X		X		X		X		X		X		X	X	X	
Blood chemistry	X	X		X		X		X		X		X		X	X	X	
Serum IgG	X									X					X	X	

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Study Procedure	**Screening**	**Induction Treatment Period**												**Maintenance (M) Treatment Period[23]**	**Follow-up[2]**		
Cycle / Maintenance	**Screening[1]**	**Cycle 1**		**Cycle 2**		**Cycle 3**		**Cycle 4**		**Cycle 5**		**Cycle 6**		**M1 to M12**	**Clinical Follow-up** **90 Days Post Last Dose**	**Clinical Q12W Follow-up**	**Survival Follow-up**
Visit Day	**D-28 to -1**	**D1**	**D2**	**D1**	**D2**	**D1**	**D2**	**D1**	**D2**	**D1**	**D2**	**D1**	**D2**	**D1 (Q8W)**	**D1**	**D1 (Q12W)**	**D1 (Q12W)**
Visit Window		**±2 days**		**±2 days**		**±2 days**		**±2 days**		**±2 days**		**±2 days**		**±2 days**	**±7 days**	**±7 days**	**±7 days**
PT (INR)/PTT or aPTT[9]	X									X							
CMV PCR[11]	X									X							
HIV, HCV, HBV[10]	X																
Serum beta 2 microglobulin	X																
Urinalysis	X																
Pregnancy test[12]	X	X		X		X		X		X		X		X	X		
Tumor Assessments/Efficacy[13]																	
CT or MRI[14]	X	W12 (± 14 days), W24 (±14 days), W36 (± 14 days), W48 (± 14 days), W72 (± 14 days), W96 (± 14 days) and W120 (± 14 days) followed by a clinical 90 day follow-up visit (±14 days), Q12W (± 14 days) at first 3 clinical Q12W follow-up visits, and Q24W (±14 days) thereafter, until progression, start of non-protocol anti-lymphoma therapy or at any time when disease progression is suspected.														X[2c]	
PET-CT[15]	X	If positive at screening, FDG-PET is required in all the timepoints corresponding to CT or MRI assessments (see above).														X[2c]	
BMA/BMBx[16]	X	To confirm CR (if positive as screening) or PD and per as per discretion of investigator.														X[2c]	
Lymph node/tumor biopsy[17]	X	X (If Progressive Disease)															
Biomarker Sampling[20]																	

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Study Procedure	**Screening**	**Induction Treatment Period**												**Maintenance (M) Treatment Period[23]**	**Follow-up[2]**		
Cycle / Maintenance	**Screening[1]**	**Cycle 1**		**Cycle 2**		**Cycle 3**		**Cycle 4**		**Cycle 5**		**Cycle 6**		**M1 to M12**	**Clinical Follow-up** **90 Days Post Last Dose**	**Clinical Q12W Follow-up**	**Survival Follow-up**
Visit Day	**D-28 to -1**	**D1**	**D2**	**D1**	**D2**	**D1**	**D2**	**D1**	**D2**	**D1**	**D2**	**D1**	**D2**	**D1 (Q8W)**	**D1**	**D1 (Q12W)**	**D1 (Q12W)**
Visit Window		**±2 days**		**±2 days**		**±2 days**		**±2 days**		**±2 days**		**±2 days**		**±2 days**	**±7 days**	**±7 days**	**±7 days**
Cytokine profiling (serum)		See detailed Table 27															
Peripheral immunophenotyping		See detailed Table 27															
ctDNA sample		See detailed Table 27															
Blood collection - genomic DNA (optional)[19]		X															
Patient-reported Outcome Assessment[19]																	
EORTC-QLQ-C30		X		X		X		X		X		X		X	X	X	
EQ-5D-5L		X		X		X		X		X		X		X	X	X	
FACT-LymS		X		X		X		X		X		X		X	X	X	
PGIS		X		X		X		X		X		X		X	X	X	
PGIC				X		X		X		X		X		X	X	X	
GP5 (from FACT-G Questionnaire)				X		X		X		X		X		X			

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Study Procedure	**Screening**	**Induction Treatment Period**												**Maintenance (M) Treatment Period[23]**	**Follow-up[2]**		
Cycle / Maintenance	**Screening[1]**	**Cycle 1**		**Cycle 2**		**Cycle 3**		**Cycle 4**		**Cycle 5**		**Cycle 6**		**M1 to M12**	**Clinical Follow-up** **90 Days Post Last Dose**	**Clinical Q12W Follow-up**	**Survival Follow-up**
Visit Day	**D-28 to -1**	**D1**	**D2**	**D1**	**D2**	**D1**	**D2**	**D1**	**D2**	**D1**	**D2**	**D1**	**D2**	**D1 (Q8W)**	**D1**	**D1 (Q12W)**	**D1 (Q12W)**
Visit Window		**±2 days**		**±2 days**		**±2 days**		**±2 days**		**±2 days**		**±2 days**		**±2 days**	**±7 days**	**±7 days**	**±7 days**
Survival																	
Survival monitoring (can be done via phone)																	X

aPTT=Activated partial thromboplastin time; BMA=Bone marrow aspiration; BMBx=Bone marrow biopsy; CHOP=Cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone; CT=Computed tomography; ctDNA=circulating tumor DNA; CVP=cyclophosphamide, vincristine, and prednisone/prednisolone; D=Day; DNA=Deoxyribonucleic acid; ECG=Electrocardiogram; Echo=Echocardiogram; ECOG=Eastern Cooperative Oncology Group; EORTC QLQC30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; EQ-5D-5L=EuroQoL-5 Dimension-5 Level Scale; FACT-Lym=Function Assessment of Chronic Illness Therapy General/ lymphoma-specific subscale; FDG-PET = 18F-fluorodeoxyglucose-positron emission tomography, HBV=Hepatitis B virus; HCV=Hepatitis C virus; HIV=Human immunodeficiency virus; Ig=Immunoglobulin; INR=International normalized ratio; IV=Intravenous; max=Maximum; MRI=Magnetic resonance imaging; MUGA=Multi-gated acquisition scan; PET-CT=Positron emission tomography-computed tomography; PGIS=Patient Global Impression of Severity; PGIC=Patient Global Impression of Change; PO=By mouth; PT=Prothrombin time; PTT=Partial thromboplastin time; Q4W=Every 4 weeks; Q12W=Every 12 weeks; W=Week

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9.1.1. Footnotes for the Schedule of Events Table 21 (Odronextamab Arm), Table 20 (Odronextamab Arm – Follow-Up Period), Table 22 (Rituximab-CHOP/CVP Arm), and Table 23 (Rituximab + Bendamustine Arm)

1. Screening window: If the screening clinical assessments are performed within 72 hours of C1D1, the C1D1 assessment does not need to be repeated.
2. Follow-up period:
   a. Follow-up starts after the last dose of study drug with a clinical follow-up after 90 days or up to the start of new anti-lymphoma therapy or withdrawal of consent by participant, whichever is earlier. Subsequent follow-up visits will be Q12W. The clinical Q12W follow-up visits are only applicable for participants that discontinued treatment for reasons other than disease progression and occur up to the start of new anti-lymphoma therapy or withdrawal of consent by participant, whichever is earlier. Survival follow-up visits may be done remotely (e.g., by phone call).
   b. If a participant discontinued treatment due to clinical or radiologic disease progression: follow-up assessments include the clinical follow-up visit 1 (up to 90 days after the last dose) and the survival follow-up visits.
   c. If a participant discontinued treatment due to reasons other than clinical or radiologic disease progression: follow-up assessments include the clinical follow-up visit 1 (at 90 days after the last dose), protocol required clinical Q12W follow-up visits (which include tumor assessments), and the survival follow up visits.
   d. Post-treatment clinical Q12W follow-up visits (Q12W) should occur in-person.
3. Participants who agree to participate in the optional genomics sub-study will be required to sign a separate sub-study ICF before collection of the sample. If a participant is re-screened on study protocol, he or she will be required to re-sign the ICF.
4. A complete physical exam is required only at Screening and includes a lymphatic exam. Thereafter, a limited physical exam and a lymphatic examination may be performed at subsequent visits. If the physical exam is performed within 72 hours prior to cycle 1 day 1, the assessment does not have to be repeated on cycle 1 day 1.
5. For doses during cycle 1 (step-up dosing), vital signs will be assessed and documented prior to the assigned treatment administration and then hourly (±15 minutes) until 4 hours following end of infusion (EOI). For participants experiencing CRS (any grade), vital signs will be assessed at least every hour (±30 minutes) until resolution of clinical symptoms. Additional monitoring may be required as clinically indicated. For doses during cycle 2 day 1 and beyond (first full dose or beyond), vital signs will be assessed and documented prior to assigned treatment administration and 1 hour after (±15 minutes), following EOI. Vital signs will also be assessed on days of the chemotherapy infusion (for investigator choice arm). During study visits where no study drug is administered, vital signs are required once at any time during the visit, and pulse oximetry is not required on these days. When scheduled at the same time as other procedures, vital signs should be measured prior to clinical laboratory assessments, PK, or exploratory sample collection.
6. Adverse events and SAEs should be collected throughout the study. All AEs are to be reported up to 90 days post last dose or start of new therapy for lymphoma, whichever

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comes first. After this period, only SAEs considered by investigator to be related to study drug will be collected.

7. Concomitant medications and procedures should be recorded from date of signed ICF up to 90 days post last study drug administration. Any treatments started after 90 days of the last dose should also be recorded only if administered to treat AEs considered by the investigator to be related to the study drug.
8. Study participants must be closely monitored for at least 24 hours (±4 hours) beyond the end of each split infusion during cycle 1 (step-up dosing). During the period of close monitoring, participants must be at the treating facility with access to emergency resuscitation equipment and medications (including epinephrine, corticosteroids, tocilizumab, etc.) available for immediate use, or participants should be within approximately 20 minutes of such a treating facility. Participants should be instructed to return to the treating facility or seek urgent medical evaluation for any symptoms of CRS, neurologic symptoms, or other symptoms they find concerning. Starting from C2D1 (first full dose) of odronextamab, close monitoring for observation of CRS signs and symptoms is no longer required, unless participant experienced a prior CRS event.
9. INR/PTT/aPTT are to be measured at Screening and cycle 5 day 8 (odronextamab) and cycle 5 day 1 (rituximab arm). See details in Section 9.2.3.8 of the protocol.
10. HIV, HBV, and HCV testing will be performed at Screening. Uncontrolled infection, as detailed in Section 9.2.3.8 of the protocol and Exclusion Criterion 10, would render a patient ineligible for enrollment in the study.
11. CMV PCR screening will be performed at Screening and cycle 5 day 8 (odronextamab arm) and cycle 5 day 1 (rituximab arm); if positive, the participant needs to be treated with an appropriate antiviral treatment until PCR testing is negative at two occasions separated by at least 1 week.
12. Pregnancy test is required in WOCBP; a serum ß-human chorionic gonadotropin (HCG) must be obtained at Screening within 72 hours of first study drug administration. Urine pregnancy test is required prior to each cycle of the chemotherapy administration (starting on cycle 1 day 8).
13. Tumor assessment scans should be performed on schedule even if there is an interruption in treatment, and the schedule for scans may not align with treatment weeks. If the participant discontinued treatment due to reasons other than clinical or radiologic disease progression, tumor assessments should be performed per clinical Q12W follow-up visit schedule.
14. Computed tomography (CT): Diagnostic quality CT with contrast (unless contrast is contraindicated) or MRI, if CT is not feasible, is required during Screening, W12 (± 14 days), W24 (± 14 days), W36 (± 14 days), W48 (± 14 days), W72 (± 14 days), W96 (± 14 days), and W120 (± 14 days) followed by the clinical 90 day visit (±14 days), Q12W (± 14 days) during the Clinical Q12W Follow-up visits 1, 2, and 3, and Q24W (±14 days) thereafter, until progression, start of non-protocol anti-lymphoma therapy, or at any time when disease progression is suspected.

15. Fluorodeoxyglucose positron emission tomography plus computed tomography (FDG-PET-CT) will be performed at screening. If negative at screening, there is no need to repeat it. If positive at screening, FDG-PET is required at all the timepoints corresponding to CT or MRI assessments: W12 (± 14 days), W24 (±14 days), W36 (± 14 days), W48 (± 14 days), W72 (± 14 days), W96 (± 14 days), and W120 (± 14 days) followed by a clinical 90 day visit (±14 days), Q12W (± 14 days) at first 3 clinical Q12W follow-up visits and Q24W (±14 days) thereafter, until progression, start of non-protocol anti-lymphoma therapy or at any time when disease progression is suspected
16. Bone marrow aspirate (BMA) and/or bone marrow biopsy (BMBx) will be performed at Screening. All bone marrow evaluations after Screening will be required only if evidence of disease is present in the bone marrow at screening assessment (evidence of bone marrow disease may be established by conventional pathology or by assessment of MRD). Wherever possible, repeat of bone marrow evaluation should be timed to coincide with CT/MRI/PET-CT scans.
17. Screening lymph node and/or tumor biopsy must be submitted to the sponsor. If fresh biopsy is not available, archival tissue not older than 18 months may be submitted. A biopsy is also requested at progressive disease if, at the discretion of the investigator, the participant has an accessible lesion, and the sample can be obtained without significant risk to the participant. Additional tumor biopsies may be performed if clinically indicated and should be submitted to the sponsor as well.
18. A blood sample for optional genomic DNA extraction will be collected prior to the first dose of odronextamab. If a sample is not obtained at that timepoint, a single sample may be collected at any other study visit, provided the participant consents. Only one sample is requested.
19. Patient-reported outcomes (PROs) are to be assessed at the indicated timepoints, before any other study procedure is performed.
20. Additional lab samples may be collected at any time to further investigate safety after discussion between the investigator and the sponsor medical director. In the odronextamab arm, if an immune-mediated adverse event is suspected, additional cytokine and peripheral immunophenotyping samples should be collected daily for the duration of the event. A ctDNA sample should also be collected at the time of disease progression. For details regarding optional DNA (PGx) sample, see Footnote 18.
21. 12-lead ECG will be performed additionally as clinically indicated.
22. Each induction cycle is 21 days for Rituximab-CHOP/CVP arm and 28 days for Rituximab-Bendamustine.
23. For odronextamab, maintenance dosing starts 6 weeks after cycle 6 day 15 dosing, and for rituximab, maintenance dosing starts 8 weeks after cycle 6 day 1 dosing.
24. For odronextamab arm only: On cycle 1 day 1, prior to dose, a baseline neurological and mental status exam is required. The following domains should be tested: orientation, naming, following commands, writing, and attention (ICE-Tool) per Table 19. Exam is required to be repeated at any time a participant has an ICANS or neurologic AE.

9.1.2. Detailed Sample Collection Timepoints

Table 27: Schedule of Events: Detailed Sample Collection Timepoints for Pharmacokinetics, Immunogenicity, and Biomarkers

Cycle or Maintenance[1]	Visit	Timepoint	PK[2,4,5]	ADA[2,5]	Peripheral Immuno-phenotyping[3,6]	Cytokines[3,6]	ctDNA[3,6,7]
Part 1: Cycles 1 and 2							
C1 Part 1	D1	PRE	x	x	x	x	x
		EOI	x			x	
	D2	PRE	x		x	x	
		EOI	x			x	
	D8	PRE	x		x	x	
		EOI	x			x	
	D9	PRE	x		x	x	
		EOI	x			x	
	D15	PRE	x		x	x	
		EOI	x			x	
	D16	PRE	x		x	x	
		EOI	x			x	
C2 Part 1 (Cycle 3+ is described below)	D1	PRE	x		x	x	
		EOI	x			x	
Part 2: Cycles 1 and 2							
C1 Part 2	D1	PRE	x	x	x	x	x
		EOI	x			x	
	D8	PRE	x			x (odro arm only)	
		EOI	x			x (odro arm only)	
	D15	PRE	x			x (odro arm only)	
		EOI	x			x (odro arm only)	
C2 Part 2 (Cycle 3+ is described below)	D1	PRE	x				

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Cycle or Maintenance[1]	Visit	Timepoint	PK[2,4,5]	ADA[2,5]	Peripheral Immuno-phenotyping[3,6]	Cytokines[3,6]	ctDNA[3,6,7]
Part 1 and 2: Cycle 3+							
C3	D1	PRE	x				x
		EOI	x				
C4	D15	PRE	x	x			
		EOI	x				
C5	D8	PRE	x				
		EOI	x				
C6	D1	PRE	x				x
		EOI	x				
	D15	PRE	x				
		EOI	x				
M1	D1	PRE	x	x	x		x
		EOI	x				
M2	D1	PRE	x				x
		EOI	x				
M3	D1	PRE	x	x			x
		EOI	x				
M4	D1	PRE	x				
		EOI	x				
M5	D1	PRE	x		x		x
		EOI	x				
M6	D1	PRE	x	x			
		EOI	x				
M7	D1	PRE	x				x
		EOI	x				
M8	D1	PRE	x				
		EOI	x				
M9	D1	PRE	x	x			x
		EOI	x				
M10	D1	PRE	x				

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Cycle or Maintenance[1]	Visit	Timepoint	PK[2,4,5]	ADA[2,5]	Peripheral Immuno-phenotyping[3,6]	Cytokines[3,6]	ctDNA[3,6,7]
		EOI	x				
M11	D1	PRE	x				
		EOI	x				
M12	D1	PRE	x	x	x		x
		EOI	x				
Follow-up 90 Days Post Last Dose		Any time	x	x	x		x
Clinical Q12W follow-up Post Last Dose		Any time	x (W24 only)		x (W24, W48, W96)		x[7]

ADA=antidrug antibodies; C=Cycle; D=Day; EOI=End of infusion; FU=Follow-up; PK=pharmacokinetics; M=Maintenance; PRE=Predose; W= Week
Note: samples need to be collected again when doses are repeated.

9.1.2.1. Footnotes for Detailed Sample Collection Timepoints for Pharmacokinetics, Immunogenicity, and Biomarkers

1. For participants in the odronextamab study arm and rituximab+CHOP / rituximab+CVP study arm, cycle 1 through cycle 6 consist of 3-week (21-day) blocks of time. For participants in the rituximab+bendamustine study arm, cycle 1 through cycles 6 consist of 4-week (28-day) blocks of time. For all study participants, the maintenance period (M1 through M12) consists of 8-week (56-day) blocks of time.
2. Participants in the odronextamab study arm will have blood samples collected for odronextamab concentration (PK) and immunogenicity (ADA) assessments in serum. Predose PK and ADA samples are to be collected prior to odronextamab dosing. For all samples, regardless of infusion duration, the EOI is the time when all of the odronextamab present in the IV bag and IV line has been infused. Sample collection instruction: predose PK and ADA samples should be collected within 2 hours prior to starting odronextamab infusion and the EOI PK samples collected within 1 hour after EOI of odronextamab. The actual dosing time and sample collection time must be recorded.
3. Except for where indicated, predose cytokine and peripheral immunophenotyping samples are to be collected from all participants before any drug is administered. For all samples, regardless of infusion duration, the EOI is the time when all of the odronextamab present in the IV bag and IV line has been infused. Sample collection instruction: predose cytokine, peripheral immunophenotyping and ctDNA (within 2 hours prior to starting infusion of the first chemotherapy drug) and EOI (+ 30 mins). The actual dosing time and sample collection time must be recorded.
4. PK samples should be drawn from the opposite arm rather than from the IV line for odronextamab administration to ensure accuracy of measured drug concentration in serum

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and to avoid sample contamination. In a special case that samples cannot be drawn from the opposite arm and need to be drawn from the IV line for odronextamab administration, the IV line needs to be flushed, and the first sample collected must be discarded before collecting any PK samples; the case must be documented accordingly.

5. In the event of an AESI due to IRRs or hypersensitivity, additional PK and ADA samples may be collected at or near the onset when possible, using unscheduled kits. The actual sample collection time must be recorded.
6. Cytokine samples in the rituximab with chemotherapy arms should be collected on cycle 1 day 1 only. In this arm, peripheral immunophenotyping and ctDNA should be collected on the same schedule as the Part 2 odronextamab arm. In the odronextamab arm, if an immune-mediated AE is suspected, additional cytokine and peripheral immunophenotyping samples should be collected daily for the duration of the event.
7. A ctDNA sample should also be collected at the time of disease progression.

9.1.3. Changes to the Schedule of Events/Study Procedures in Case of Dose Modification

General guidance: Treatment cycles are numbered continuously and align with any dose administered, regardless of whether the actual dose was according to the per-protocol dosing regimen or from a dose modification.

For scenarios where the dosing administration differs from per-protocol dosing regimen:

- For initial dose, intermediate dose 1, intermediate dose 2, and the first full QW dose of odronextamab, sites should follow cycle 1 days 1 and 2, days 8 and 9, days 15 and 16, and cycle 2 day 1, respectively, for close monitoring, safety monitoring, and laboratory tests. For cycle 2 day 1 close monitoring is only necessary if CRS is observed during cycle 1 (see Section 9.2.3.1).
- Close monitoring, safety monitoring, and laboratory tests also apply to any modified doses during the step-up dosing.

If any of the per-protocol specified initial dose, intermediate dose 1, intermediate dose 2 are repeated or first full QW dose administered at a delayed treatment timepoint, the below study procedures should remain on the treatment cycle/day schedule:

- physical exam
- 12-lead ECG
- ECOG
- B symptoms
- pregnancy test
- urinalysis
- serum IgG

For PK and Biomarker samples:

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- Sample collection during the visits where the initial dose, intermediate dose 1, intermediate dose 2, and the first full QW dose of study drug are administered for the first time. (This includes when the participant receives only first split in prior week and has to repeat the dose again.)
  - PK and biomarker blood samples: Will be collected according to the treatment cycle/day schedule of events that correspond to the particular step-up dose.
- When patients have paused and resumed treatment, samples must be collected as per the following.
  - PK samples: For any repeated doses, only the pre-dose and EOI PK samples will be collected.
  - Biomarker blood samples: For any repeated dose, samples will be collected again according to the treatment cycle/day Schedule of Events that correspond to the particular step-up dose.

9.1.4. Unscheduled Visits

All attempts should be made to keep participants on the study schedule. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, or for any other reason, as warranted.

Relevant assessments that occur during unscheduled visits should be reported in the respective eCRF for the visit date.

9.2. Study Procedures

9.2.1. Procedures Performed Only at the Screening/Baseline Visit

The following procedures will be performed for the sole purpose of determining study eligibility or characterizing the baseline population:

- Informed consent
- Genomics informed consent
- Demographics
- Inclusion/exclusion criteria
- Medical/oncology history review
- Concomitant medications/procedures review
- Complete physical examination
- Height and weight
- For all participants, a local histopathology review of tissue will be conducted before study enrollment. Eligibility for this study will be confirmed upon establishing a diagnosis of FL grade 1 to 3a.
  - Corresponding tumor biopsy should also be sent to central laboratory.

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- Brain MRI or CT: During screening (within 28 days prior to start of study drug administration), a mandatory brain MRI will be performed to evaluate for evidence of CNS involvement of malignancy and/or for other findings that might preclude inclusion in the trial according to the protocol eligibility criteria. If brain MRI is infeasible, a CT scan may be substituted if approved by the sponsor.
  - If imaging is performed during treatment or follow-up period as part of standard of care, data will also be collected.
- Vital signs
- ECOG performance
- B symptoms assessment
- Echocardiogram or MUGA (cardiac ejection fraction)
- 12-lead ECG
- Routine safety laboratory tests
- Viral serologies: HIV, HBV, HCV testing
- CMV PCR
- Serum beta 2 microglobulin
- Serum IgG

Participants who fail screening may be screened one additional time, and an ICF will need to be signed at the re-screen. Some procedures (CT/MRI scans, FDG-PET-CT scan) may not need to be repeated if they were previously completed within 28 days prior to the first dose.

9.2.2. Efficacy Procedures

9.2.2.1. Radiographic Disease Assessment

For all participants, disease will be radiologically evaluated according to the Lugano Classification (Cheson, 2014b) for the primary endpoint of CR30 (Shi, 2017) based on independent central review and for the secondary endpoint as determined by investigator review. The CT or MRI for tumor assessment will be performed as detailed below.

All radiological imaging will be submitted to a central repository and will be reviewed centrally.

9.2.2.1.1. Computed Tomography Imaging/Magnetic Resonance Imaging

A diagnostic quality (≤5 mm slices) MRI or CT scan with contrast of the neck, chest, abdomen, and pelvis as well as any other known sites of disease will be performed according to the schedule in Table 23 , Table 25 and Table 26 and at any time when disease progression is suspected. All measurable and evaluable lesions should be assessed and documented. A mandatory imaging of the brain at baseline should be performed as described in Section 9.2.1.

For each participant, the same method of measurements and the same technique must be used to evaluate disease burden throughout the study. If a participant inadvertently misses a prescribed tumor evaluation or a technical error prevents the evaluation, the participant may continue

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treatment until the next scheduled assessment, unless signs of clinical progression are present. If at any time during the treatment period, there is suspicion of disease progression based on clinical or laboratory findings (and before the next scheduled assessment), an unscheduled tumor assessment should be performed. Details of the imaging procedures can be found in the imaging manual.

9.2.2.1.2. ^{18}F-Fluorodeoxyglucose-Positron Emission Tomography

^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET) scans will also be performed as per the schedule in Table 23 , Table 25 and Table 26. If FDG-PET is negative at screening, it does not need to be repeated. The CT portion of the FDG-PET-CT cannot replace a diagnostic quality CT/MRI scan, unless it is of diagnostic quality. For participants with FDG-PET avid disease at screening, both diagnostic CT/MRI and FDG-PET are required at the applicable timepoints. More detailed information is provided in the imaging manual.

9.2.2.2. Bone Marrow Aspirate and Bone Marrow Biopsy

For all participants, a bone marrow aspirate and/or biopsy (BMA/BMx) will be performed as described in Table 23, Table 25 and Table 26. Additional bone marrow exams should be performed as clinically indicated by the investigator. Samples obtained from BMA/BMx will be evaluated locally at the site according to institutional standard practices. Samples will also be shipped to the central laboratory and will be utilized for additional research testing (Section 9.2.6). Detailed instructions for sample collection and preparation are provided in the laboratory manual.

9.2.2.3. Lymph Node/Tumor Biopsy

Lymph node/tumor biopsy will be performed at visits specified in Table 23 , Table 25 and Table 26. Samples will be sent for local analysis (flow, immunohistochemistry, molecular/cytogenetic analysis), and a sample will also be submitted to the central laboratory, as specified in the laboratory manual. Additional tumor biopsies may be performed if clinically indicated (e.g. tumor swelling after administration of odronextamab) or as part of standard of care. For these additional biopsies, the collection of local analysis information in the CRF is requested, and a sample will also be submitted to the central laboratory. Detailed instructions for sample collection and preparation are provided in the laboratory manual.

The tumor will be analyzed for changes in biomarkers of interest, including number and distribution of activated T cells, CD20 expression, expression of checkpoint modulators, etc. Additional analyses including but not limited to tumor RNA expression and tumor DNA may also be performed. When feasible, single cell analysis (flow cytometry, RNAseq, TCR seq) will also be performed.

9.2.2.4. Patient-Reported Outcome Measures

Patient-reported outcomes will be measured at a frequency indicated in Table 23, Table 24 Table 25 and Table 26 using electronic patient self-administered EORTC-QLQ-C30, FACT-LymS, EQ-5D-5L, FACT-G GP5, PGIC, and PGIS questionnaires/questions. Participants will be asked to complete these questionnaires prior to any study procedures being performed at a given study visit.

9.2.2.4.1. European Organization for the Research and Treatment of Cancer: Quality of Life of Cancer Patients Questionnaire-30 (EORTC-QLQ-C30)

The EORTC QLQ-C30 is an internationally validated and widely used cancer-specific HRQOL instrument. It contains five functional scales (physical, social, role, cognitive, and emotional functioning), eight symptom scales/items (fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, and diarrhea), financial difficulties, and global health status/QoL. For the functioning scales and global health status/QOL, higher scores indicate better functioning; for the symptom scales, higher scores indicate higher symptom burden.

9.2.2.4.2. Assessment of Lumps

Based on a PRO conceptual model developed for FL patients, lumps were found to be an important concept/symptom to patients. To assess the bother of lumps, an individual question has been developed – "Have you been bothered by lumps," with a 4-point scale aligned to the EORTC Item library utilized for responses.

9.2.2.4.3. Functional Assessment of Cancer Treatment-Lymphoma; Lymphoma Subscale (FACT-LymS)

The FACT-Lym is composed of the generic questionnaire FACT-G plus the 15-item lymphoma subscale (LymS) and was developed in 2005. The questionnaire addresses health-related quality of life issues for NHL patients. Only the lymphoma subscale will be utilized in this study to supplement the functional and symptom assessment from EORTC-QLQ-C30.

9.2.2.4.4. EQ-5D-5L

The EQ-5D-5L is the 5-level version of EQ-5D introduced in 2009 by the EuroQol Group. The EQ-5D-5L consists of the EQ-5D descriptive system and the EQ visual analog scale (EQ VAS). The EQ-5D-5L descriptive system comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The EQ VAS records the participant's self-rated health on a vertical visual analog scale, where the endpoints are labelled "Best imaginable health state" and "Worst imaginable health state."

9.2.2.4.5. Patient's Global Impression of Change and Patient's Global Impression of Severity

Two global anchors, the PGIC and PGIS, will be used to aid in the interpretation of EORTC QLQ-C30, FACT-Lym, and EQ-5D-5L results. The PGIC is a single item used to evaluate all aspects of patients' health and assesses if there has been an improvement or decline in clinical status. The PGIS is a single item used to evaluate participants' perception of disease severity.

9.2.2.4.6. Functional Assessment of Cancer – General (FACT-G) GP5 Item

A single item (GP5) of the validated FACT-G questionnaire will be used to assess (from the participant's perspective) the overall impact of treatment toxicity, based upon its association with the number and degree of adverse events.

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9.2.3. Safety Procedures

9.2.3.1. Safety Monitoring

Post-infusion safety monitoring of participants will include but will not be limited to vital signs (with specific attention to temperature and blood pressure), oxygen saturation, and clinical assessments.

Study participants must be closely monitored for at least 24 hours (±4 hours) beyond the end of each split infusion during cycle 1 (step-up dosing). During the period of close monitoring, participants must be at the treating facility with access to emergency resuscitation equipment and medications (including epinephrine, corticosteroids, tocilizumab, etc.) available for immediate use, or participants should be within approximately 20 minutes of such treating facility. Participants should be instructed to return to the treating facility or seek urgent medical evaluation for any symptoms of CRS, neurologic symptoms, or other symptoms they find concerning. Starting from C2D1 (first full dose) of odronextamab, close monitoring for observation of CRS signs and symptoms is no longer required, unless participant experienced a prior CRS event.

9.2.3.2. Vital Signs

Vital signs, including temperature, blood pressure, pulse, pulse oximetry, and respiration rate, will be collected pre-dose at timepoints according to Table 23, Table 24 Table 25 and Table 26.

Note: Blood pressure should be measured after the patient has been resting quietly for at least 5 minutes. Blood pressure measurements should be obtained from a seated or recumbent position and should be performed consistently throughout the study.

9.2.3.3. Body Weight

Body weight will be assessed using calibrated scales. Participants should void (empty bladder) prior to weight assessment. Body weight will be recorded to the nearest 0.1 kg.

9.2.3.4. Physical Examination

A physical examination will be performed at study visits according to Table 23, Table 24 Table 25 and Table 26. Complete physical examination will include examination of skin, head, eyes, nose, throat, neck, joints, lungs, heart, pulse, abdomen (including liver and spleen), lymph nodes, and extremities, as well as a brief neurologic examination.

A complete physical is required as a part of screening assessments. Limited physical examination that includes lungs, heart, abdomen, lymph node, and skin may be performed instead of a complete physical on other assessment days.

Care should be taken to examine and assess any abnormalities that may be present, as indicated by the patient's medical history or AE.

9.2.3.5. Electrocardiogram

Electrocardiograms should be performed before blood is drawn during visits requiring blood draws. A standard 12-lead ECG will be performed at screening and if clinically indicated, please refer to Table 23, Table 24 Table 25 and Table 26. Heart rate will be recorded from the ventricular

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rate, and the PR, QRS, RR, and QT (identify QTcB or QTcF) intervals will be recorded. The ECG strips and reports will be retained with the source.

9.2.3.6. Performance Status

Performance status will be assessed according to ECOG criteria.

9.2.3.7. Assessment for B Symptoms

Assessment of B symptoms will occur as part of the clinical assessment. B symptoms include:

- Fever (ie, temperature >38°C [>100.4°F]) for 3 consecutive days
- Weight loss exceeding 10% of body weight in 6 months
- Drenching night sweats

9.2.3.8. Laboratory Testing

Samples for laboratory testing will be collected at visits according to Table 23, Table 24 Table 25 and Table 26. Detailed instructions for blood sample collection are in the laboratory manual provided to study sites.

- Hematology, blood chemistry, urinalysis, additional clinical laboratory tests (e.g. pregnancy testing, serum IgG testing, HIV/HCV/HBV/CMV, INR/PTT, or aPTT) will be analyzed by a local laboratory.
- Cytokines, peripheral immunophenotyping, ctDNA, and optional DNA samples will be analyzed by the central laboratory. PK and ADA samples will be assessed by an external laboratory.
- Lymph node/tumor biopsy samples and BMA/BMBx samples will be sent for analysis to both the local laboratory and the central laboratory.

Tests will include:

Blood Chemistry

Sodium	Total protein, serum	Total and direct bilirubin
Potassium	Creatinine	Total cholesterol
Chloride	Blood urea nitrogen (BUN) or Urea	Triglycerides
Carbon dioxide	Aspartate aminotransferase (AST)	Uric acid
Calcium	Alanine aminotransferase (ALT)	Creatine phosphokinase (CPK)
Glucose	Alkaline phosphatase	
Albumin	Lactate dehydrogenase (LDH)	

Hematology

Hemoglobin	Differential:
Hematocrit	Neutrophils
Red blood cells (RBCs)	Lymphocytes
White blood cells (WBCs)	Monocytes
Red cell indices	Basophils

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Platelet count	Eosinophils

Urinalysis

RBC
WBC
Blood
Glucose
Ketones
Protein

Other Laboratory Tests

Pregnancy test: Serum β-HCG will be measured at screening (≤72 hours prior to first dose of study drug administration), and urine or serum β-HCG will be measured at all other time points.

Serum Calcium Corrected for Albumin (derived): Levels of unbound/free calcium (ie, biologically active calcium) will be calculated by adjusting for abnormal albumin levels ("corrected serum calcium").

Creatinine clearance (derived): Calculated based on serum creatinine by the Cockcroft-Gault formula or from 24-hour urine collection.

Coagulation: Assessed by activated partial thromboplastin time (aPTT) or partial thrombin time (PTT) and International Normalized Ratio (INR).

Immunoglobulin (IgG): Serum IgG will be evaluated.

HIV, HCV, and HBV Testing: Participants will be tested for HIV, HCV, and HBV during screening if they were known to be positive prior to screening. Presence of positive test results for HIV, hepatitis B (HB virus [B DNA], HB surface antigen [HBsAg], total core HB antibody [anti-HB-c]), or hepatitis C virus (HCV antibody serology testing) will require evaluation by molecular methodologies to assess viral load.

CMV Testing: Participants will be assessed for CMV infection with a peripheral blood PCR assay at screening. CMV PCR must be undetectable prior to enrollment. PCR surveillance will continue on therapy at pre-specified timepoints and as clinically indicated.

Abnormal Laboratory Values and Laboratory Adverse Events

All laboratory values must be reviewed by the investigator or authorized designee.

Significantly abnormal test results that occur after start of treatment must be repeated to confirm the nature and degree of the abnormality. When necessary, appropriate ancillary investigations should be initiated. If the abnormality fails to resolve or cannot be explained by events or conditions unrelated to the study medication or its administration, the medical/study director must be consulted.

The clinical significance of an abnormal test value within the context of the disease under study must be determined by the investigator.

Criteria for reporting laboratory values as an AE are provided in Section 10.1.1.

9.2.3.9. Adverse Events

At every visit, AEs will be assessed and recorded as described in Section 10.

9.2.4. Drug Concentration and Measurements

Blood samples for the assessment of odronextamab concentrations in serum will be collected over time, as listed at timepoints according to Table 27. Actual sample collection times will be recorded. Detailed instructions for blood sample collection are provided in the laboratory manual.

Any unused samples may be used for exploratory research, biomarker research, and/or future biomedical research.

9.2.5. Immunogenicity Measurements and Samples

Blood samples for immunogenicity assessment (ADA and NAb) in serum will be collected at timepoints according to Table 27. Detailed instructions for blood sample collection are provided in the laboratory manual.

Any unused samples may be used for exploratory research, biomarker research, and/or future biomedical research (FBR).

9.2.6. Pharmacodynamic and Exploratory Biomarker Procedures

Cytokine upregulation triggered by target engagement may reflect T-cell activation. Understanding the magnitude and time course of pharmacodynamic changes in serum cytokines may inform dosing and help understand and manage possible safety signals. Serum samples collected for cytokine analysis may also be used to explore additional biomarkers of interest (for example, other inflammatory factors).

Changes in lymphocyte subsets and activation status may also be anticipated based on preclinical data and the proposed mechanism of action. Immunophenotyping of T-cell and B-cell subsets and other cell populations (including monocytes and natural killer [NK] cells) in peripheral blood (by flow cytometry) will be performed to assess potential changes with and upon completion of study drug treatment. Additional exploratory analysis on peripheral blood samples including but not limited to RNA sequencing may be conducted.

Measurable Residual Disease (MRD) will be assessed on circulating tumor DNA samples collected as described in the laboratory manual. Measurable Residual Disease is a good predictive marker of response to T-cell engagers with similar mechanism of action in acute lymphoblastic leukemia (ALL); however, this is still exploratory for NHL. In this study, changes in MRD will be monitored in blood at baseline, on treatment, and during follow-up. The purpose of this assessment is to evaluate the predictive value of MRD in participants with NHL treated with odronextamab. MRD will be assessed by next generation sequencing.

9.2.7. Future Biomedical Research (Optional)

Participants who agree to participate in the FBR sub-study will be required to consent to this optional sub-study before samples are banked for FBR. Residual biomarker samples for study-related research as well as unused PK and ADA samples will be stored for up to 15 years after the final date of the database lock (or for a shorter time period if required per regional laws and regulations). The samples may be utilized for FBR that may or may not be directly related to the

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study, including being used as reference samples and assay development or validation. The results of these future biomedical research analyses will not be presented in the CSR.

9.2.8. Pharmacogenomic Analysis (Optional)

Participants who agree to participate in the genomics sub-study will be required to consent to this optional sub-study before collection of the samples. Whole blood samples for DNA extraction should be collected on day 1/baseline (predose) but can be collected at a later study visit. DNA samples will be collected for pharmacogenomics analyses to understand the genetic determinants of efficacy and safety associated with the treatments in this study and the molecular basis of indolent lymphoma and related diseases. These samples will be single-coded as defined by the International Council on Harmonisation (ICH) guideline E15. Samples will be stored for up to 15 years after the final date of the database lock (or for a shorter time period if required per regional laws and regulations). If there are specific site or country requirements involving the pharmacogenomic analyses, which the sponsor is unable to comply with, samples will not be collected at those sites.

The purpose of the pharmacogenomic analyses is to identify genomic associations with clinical or biomarker response to odronextamab, other indolent lymphomas' clinical outcome measures and possible AEs. In addition, associations between genomic variants and prognosis or progression of indolent lymphoma as well as related oncologic diseases may also be studied. These data may be used or combined with data collected from other studies to identify and validate genomic markers related to the study drug, target pathway, or indolent lymphoma and related diseases.

Analyses may include sequence determination or single nucleotide polymorphism studies of candidate genes and surrounding genomic regions. Other methods, including whole-exome sequencing, whole-genome sequencing, DNA copy number variation, and transcriptome sequencing (or other methods for quantitating RNA expression) may also be performed. The list of methods may be expanded to include novel methodology that may be developed during the course of this study or sample storage period. Results from the genomic analyses will not be reported in the CSR.

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10. SAFETY EVALUATION AND REPORTING

10.1. Recording and Reporting Adverse Events

10.1.1. General Guidelines

The investigator must promptly record all clinical events occurring during the study per the Schedule of Events, from the time of ICF signature to the end of on-treatment period (see Section 9). From the time of ICF signature and prior to initiation of study treatment, only the following categories of AEs should be reported on the AE CRF:

- SAEs
- Non-SAEs associated with a protocol-mandated intervention (eg, AEs related to an invasive procedure such as a biopsy)

Other AEs that occur after ICF signature and prior to first treatment should be reported on the medical history CRF.

Medical conditions that existed or were diagnosed prior to the signing of the ICF will be recorded as part of medical history. Abnormal laboratory values and vital signs observed at the time of informed consent should also be recorded as medical history. Any subsequent worsening (ie, any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug should also be recorded as an AE.

At each visit, the investigator will determine whether any AEs have occurred by evaluating the participant. Adverse events may be directly observed, reported spontaneously by the participant, or by questioning the participant at each study visit. Participants should be questioned in a general way without asking about the occurrence of any specific symptoms. The investigator must assess all AEs to determine seriousness, severity, and causality in accordance with the definitions in Section 10.3. The investigator's assessment must be clearly documented in the site's source documentation with the investigator's signature. The investigator should follow up on SAEs (and AESIs) until they have resolved or are considered clinically stable; AEs should be followed until they are resolved or last study visit, whichever comes first.

Always report the diagnosis as the AE or SAE term. When a diagnosis is unavailable, report the primary sign or symptom as the AE or SAE term with additional details included in the narrative until the diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, report them as individual entries of AE or SAE.

Laboratory results, vital signs, and other diagnostic results or findings should be appraised by the investigator to determine their clinical significance. Isolated abnormal laboratory results, vital sign findings, or other diagnostic findings (ie, not part of a reported diagnosis) should be reported as AEs if they are symptomatic, lead to study drug discontinuation, dose reduction, require corrective treatment, or constitute an AE in the investigator's clinical judgment.

For events that are serious due to hospitalization, the reason for hospitalization must be reported as the SAE (diagnosis or symptom requiring hospitalization). A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE. Pre-planned (prior to signing the ICF) procedures, treatments requiring hospitalization for pre-existing conditions that do not worsen in

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severity, and admission for palliative or social care should not be reported as SAEs (see Section 10.3 for definitions).

For deaths not due to progressive disease, the underlying or immediate cause of death should always be reported as an SAE.

Progression of underlying malignancy will not be considered an AE or SAE if it is clearly consistent with the typical progression pattern of the underlying cancer (including time course, affected organs, etc.). Clinical symptoms of progression may be reported as AEs if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy or does not fit the expected pattern of progression for the disease under study. If there is any uncertainty about an AE being due only to progression of the underlying malignancy, it should be reported as an AE or SAE.

Any SAE that may occur subsequent to the reporting period (end of the on-treatment period) that the investigator assesses as related to study drugs should also be reported.

All AEs, SAEs, AESIs, and pregnancy reports are to be reported according to the procedures in Section 10.2.2.

10.2. Reporting Procedure

10.2.1. Individual Case Safety Reporting (ICSR)

All events (serious and non-serious) must be reported with the investigator's assessment of the event's seriousness, severity, and causality to the study drug. For SAEs and AESIs, a detailed narrative summarizing the course of the event, including its evaluation, treatment, and outcome should be provided on the AE CRF. Specific or estimated dates of event onset, treatment, and resolution should be included, when available. Medical history, concomitant medications, and laboratory data that are relevant to the event should also be summarized in the narrative. For fatal events, the narrative should state whether an autopsy was or will be performed, and include the results if available. Information not available at the time of the initial report must be documented in a follow-up report. Source documents (including hospital or medical records, diagnostic reports, etc.) will be summarized in the narrative on the AE CRF and retained at the study center and available upon request.

When reporting a SAE, the investigators will additionally evaluate the causal relationship with the other DUICT, which are specified in the protocol (See Section 3.2.2).

Urgent safety queries must be followed up and addressed promptly. Follow-up information and response to non-urgent safety queries should be combined for reporting to provide the most complete data possible within each follow-up.

10.2.2. Events that Require Expedited Reporting to Sponsor

The following events also require reporting to the sponsor (or designee) within 24 hours of learning of the event:

- **SAEs**
- **Selected AESIs (serious and nonserious):** AESIs for this study include the following:

  - Grade 3 or greater IRRs
  - Grade 2 or greater CRS [graded according to (Lee, 2019)]
  - Grade 3 or greater TLS
  - Grade 2 or greater ICANS events [graded as per(Lee, 2019)]
  - Grade 3 or greater allergic reactions
  - Grade 3 or greater infections
  - Grade 2 or greater CNS events
  - CMV infection
  - Hepatitis B re-activation
- Any AE that meets DLT criteria (during the DLT evaluation period of part 1)
- **Pregnancy:** Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the sponsor (or designee) within 24 hours of identification any pregnancy occurring in a female or female partner of a male during the study or within 180 days of the last dose of study drug. Any complication of pregnancy affecting a female study participant or female partner of a male study participant and/or fetus and/or newborn that meets the SAE criteria must be reported as an SAE. Outcome for all pregnancies should be reported to the sponsor.
- Overdose of odronextamab: Accidental overdose of at least 2 times the intended dose of study drug (odronextamab) within the visit window.

10.3. Definitions

10.3.1. Adverse Event

An AE is any untoward medical occurrence in a patient administered a study drug that may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease that is temporally associated with the use of a study drug, whether or not considered related to the study drug (ICH, 1994).

10.3.2. Serious Adverse Event

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

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (eg, a car accident in which a patient is a passenger).
- Is **life-threatening** – in the view of the investigator, the patient is at immediate risk of death at the time of the event. This does not include an AE that had it occurred in a more severe form, might have caused death.
- Requires in-patient **hospitalization** or **prolongation of existing hospitalization**. Inpatient hospitalization is defined as a hospital admission (any duration) or an emergency room visit for longer than 24 hours. Prolongation of existing

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hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event or is prolonged due to the development of a new AE as determined by the investigator or treating physician.

- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**.
- Is an **important medical event** – Important medical events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other serious outcomes listed above (eg, 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).

Hospitalization or death due solely to manifestations consistent with typical progression of underlying malignancy will not be considered an SAE.

Criteria for reporting SAEs must be followed for these events.

10.3.3. Adverse Events of Special Interest

An AESI (serious or non-serious) is one of scientific and medical interest specific to the sponsor's product or program for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it.

10.3.4. Severity

The severity of AEs, infusion reactions (except CRS and ICANS), and test findings classified as AEs will be graded using the NCI-CTCAE v5.0 grading system. AEs not listed in the NCI-CTCAE v5.0 will be graded according to the scale provided in Table 28.

Table 28: NCI-CTCAE Grading System (v5.0) for Adverse Events

Grade	Severity	Description
1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate	Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*
3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL†
4	Life-Threatening	Life-threatening consequences; urgent intervention indicated
5	Death	Death related to AE

* Instrumental ADLs refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

† Self-care ADLs refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not being bedridden.

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10.3.5. Causality

The investigator must provide a causality assessment as to whether or not there is a reasonable possibility that the drug caused the AE, based on evidence or facts, his/her clinical judgment, and the following definitions. The causality assessment must be made based on the available information and can be updated as new information becomes available.

The following factors should be considered when assessing causality:

- Temporal relationship: time to onset vs. time drug was administered
- Nature of the reactions: immediate vs. long term
- Clinical and pathological features of the events
- Existing information about the drug and same class of drugs
- Concomitant medications
- Underlying and concurrent illnesses
- Response to de-challenge (drug discontinuation) or dose reduction
- Response to re-challenge (re-introduction of the drug) or dose increase, when applicable
- Participant's medical and social history

Causality to the study drugs (including chemotherapy, study drug administration):

- Related:
  - The AE follows a reasonable temporal sequence from study drug administration and cannot be reasonably explained by the nature of the reaction, participant's clinical (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.

  or

  - The AE follows a reasonable temporal sequence from study drug administration and is a known reaction to the drug under study or its class of drugs or is predicted by known pharmacology.
- Not Related:
  - The AE does not follow a reasonable sequence from study drug administration or can be reasonably explained by the nature of the reaction, participant's clinical state (eg, disease under study, concurrent diseases, and concomitant medications), or other external factors.

Causality to the study conduct (protocol specified procedure):

- Related:
  - The AE follows a reasonable temporal sequence from a protocol-specified procedure and cannot be reasonably explained by the nature of the reaction,

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participant's clinical (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.

- Not Related:
  - The AE does not follow a reasonable sequence from a protocol-specified procedure or can be reasonably explained by the nature of the reaction, participant's clinical state (eg, disease under study, concurrent diseases, and concomitant medications), or other external factors.

Causality to auxiliary study medications (tocilizumab):

- Related:
  - The AE follows a reasonable temporal sequence from a protocol-specified auxiliary medication and cannot be reasonably explained by the nature of the reaction, participant's clinical (eg, disease under study, concurrent diseases, and concomitant medications), or other external factors.
- Not Related:
  - The AE does not follow a reasonable sequence from a protocol-specified auxiliary medication or can be reasonably explained by the nature of the reaction, participant's clinical state (eg, disease under study, concurrent diseases, and concomitant medications), or other external factors.

10.4. Safety Monitoring

The investigator will monitor the safety of study patient at his/her site(s) as per the requirements of this protocol and consistent with current Good Clinical Practice (GCP). Any questions or concerns should be discussed with the sponsor in a timely fashion. The sponsor will monitor the safety data from across all study sites. The medical director will have primary responsibility for the emerging safety profile of the compound but will be supported by other departments (eg, Safety; Biostatistics and Data Management). Safety monitoring will be performed on an ongoing basis (eg, individual review of SAEs) and on a periodic cumulative aggregate basis.

In addition, safety will be monitored by an IDMC on an ongoing basis as described in Section 6.3.2.

10.5. Notifying Health Authorities, Institutional Review Board/Ethics Committee, and Investigators

During the study, the sponsor and/or the contract research organization (CRO) will inform health authorities, Institutional Review Board (IRB)/Ethics Committee (EC), and the participating investigators of any suspected unexpected serious adverse reactions (SUSARs) occurring in other study centers or other studies of the active study drugs (odronextamab), as appropriate per local reporting requirements. In addition, the sponsor and/or CRO will comply with any additional local safety reporting requirements.

Upon receipt of the sponsor's notification of a SUSAR that occurred with the study drug, the investigator will inform the IRB/EC unless delegated to the sponsor.

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Event expectedness for study drug (odronextamab) will be assessed against the Reference Safety Information section of the IB that is effective for expedited safety reporting. Event expectedness for comparators (rituximab, chemotherapies: CHOP, CVP, and bendamustine) and tocilizumab will be assessed against the most recent approved SmPC for each individual drug.

At the completion of the study, the sponsor will report all safety observations made during the conduct of the trial in the CSR to health authorities and the IECs/IRB, as appropriate.

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11. STATISTICAL PLAN

This section provides the basis for the statistical analysis plan (SAP) for the study. The final SAP will be issued before the first database lock.

Endpoints are listed in Section 4. Analysis variables are listed in Section 5.

11.1. Statistical Hypothesis

In Part 2 (Randomized Phase), the primary analysis of CR30 rate will be performed for the following null (H_0) and alternative hypotheses (H_1).

H_0: The CR30 rate for odronextamab is the same as that for rituximab combined with chemotherapy.

H_1: The CR30 rate for odronextamab is different than that for rituximab combined with chemotherapy.

11.2. Justification of Sample Size

11.2.1. Part 1 (Safety Run-in)

Six (6) to 12 participants may be enrolled in each dose level; 12 evaluable participants have to be enrolled in the dose level for the recommended Part 2 dose of odronextamab. There will be up to 2 dose levels. In the event that a lower dose is selected, 8 additional participants will be enrolled to evaluate the efficacy and safety at this dose level. The total sample size in Part 1 is up to 32 participants. The actual sample size will depend on the number of DLT-evaluable participants, and the number of dose levels implemented.

The binomial probability to observe 1 or more safety events for a given true event rate in several potential sample sizes is listed in Table 29.

Table 29: Binomial Probability to Observe 1 or More Events for a Given Population Safety Event Rate

Sample size	**Population Event Rate**			
	5%	10%	15%	30%
6 participants	0.265	0.469	0.623	0.882
9 participants	0.370	0.613	0.768	0.960
12 participants	0.460	0.718	0.858	0.986
20 participants	0.642	0.878	0.961	0.999
32 participants	0.806	0.966	0.994	1.0

11.2.2. Part 2 (Randomized Phase)

The sponsor assumes a CR30 rate of 53% in participants treated with rituximab combined with chemotherapy and a CR30 rate of 68% in participants treated with odronextamab. Under these assumptions, a sample size of 446 participants will yield approximately 90% power to detect an improvement of 15% in CR30 rate with an overall 2-sided type I error of 0.05.

The assumption for CR30 rate of 53% in participants treated with rituximab combined with chemotherapy is derived from a Phase 3 RELEVANCE study of rituximab and lenalidomide versus rituximab and chemotherapy in previously untreated patients with FL (Morschhauser, 2018), where the observed CR rate at 120 weeks was 53% in the rituximab-chemotherapy arm.

The sponsor assumes the 6-year PFS rate of 59% in the rituximab-chemotherapy arm base on the RELEVANCE study results.

PFS is assumed to be distributed exponentially in both treatment groups. At the time of primary analysis for CR30, only 53% of PFS events are expected to be observed. There are no interim efficacy or futility analyses for PFS. However, a 2-sided alpha of 0.0001 will be spent at the time to control the family-wise error rate (FWER). If one interim efficacy analysis is performed for PFS, a total of 173 PFS events will yield approximately 64% power to detect an HR of 0.7 with an overall 2-sided α of 0.0499. A hazard ratio of 0.7 corresponds to an increase in 6-year PFS rate of 10.1% (59% versus 69.1%). Assuming a uniform enrollment rate of 27 participants per month and 2% dropout rate per year, enrollment of approximately 446 randomized participants will yield 173 PFS events around 95 months after the first participant is randomized.

The sponsor assumes the 6-year EFS rate of 58% in the rituximab-chemotherapy arm.

EFS is assumed to be distributed exponentially in both treatment groups. At the time of primary analysis for CR30, only 54% of EFS events are expected to be observed. There are no interim efficacy or futility analyses for EFS planned at this time. However, a 2-sided alpha of 0.0001 will be spent at the time to control the FWER. If one interim efficacy analysis of EFS is performed, a total of 177 EFS events are expected to yield approximately 65% power for an HR of 0.7 with an overall 2-sided α of 0.0499. A hazard ratio of 0.7 corresponds to an increase in 6-year EFS rate of 10.3% (58% versus 68.3%). Enrollment of approximately 446 randomized participants will yield 177 EFS events around 95 months after the first participant is randomized.

The sponsor assumes the 6-year OS rate of 89% in the rituximab-chemotherapy arm based on the RELEVANCE study results. OS is assumed to be distributed exponentially in both treatment groups. Three interim analyses of OS will be performed to evaluate the potential for harm at the time of CR30 primary, PFS interim and PFS final analyses. Each interim analysis of OS will spend 2-sided alpha of 0.0001. The information fractions are included in Section 11.5. A total of 47 OS events will yield approximately 53.3% power to detect an HR of 0.55 with an overall 2-sided α of 0.0497. A hazard ratio of 0.55 corresponds to an increase in 6-year OS rate of 4.8% (89% versus 93.8%). Assuming a uniform enrollment rate of 27 participants per month and 2% dropout rate per year, enrollment of approximately 446 randomized participants will yield 47 OS events for OS final analysis around 106 months after the first participant is randomized.

11.3. Analysis Sets

11.3.1. Efficacy Analysis Set

The Full Analysis Set (FAS) for Part 1 will include all participants who received any study drug. The efficacy analyses for Part 1 will be performed based on the FAS.

The FAS for Part 2 will include all randomized participants. The efficacy analyses for Part 2 will be performed based on the FAS according to the treatment randomized per ITT principle.

PRO analyses will be based on FAS.

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11.3.2. Safety Analysis Set

The Safety Analysis Set (SAF) will include all participants who received any study drug; it is based on the treatment received (as treated). Treatment compliance/administration and all clinical safety variables will be analyzed based on the SAF and may be performed for Part 1 and Part 2 separately.

11.3.3. Pharmacokinetic Analysis Sets

The PK analysis set includes all participants who received at least one dose of odronextamab and have at least one non-missing odronextamab concentration result following the first dose of odronextamab.

11.3.4. Immunogenicity Analysis Sets

The ADA analysis set includes all participants who received odronextamab and had at least one non-missing ADA result following the first dose of odronextamab.

The NAb analysis set includes all participants who received any study drug and who are negative in the ADA assay or with at least 1 non-missing result in the NAb assay after the first dose of study drug [participants who are ADA negative are set to negative in the NAb analysis set].

11.4. Statistical Methods

For continuous variables, descriptive statistics will include the following information: the number of participants reflected in the calculation (n), mean, standard deviation, Q1, median, Q3, minimum, and maximum.

For categorical or ordinal data, frequencies and percentages will be displayed for each category.

For time-to-event variables, median time-to-event (and the survival rate at a fixed time point) and its two-sided 95% confidence intervals will be summarized by the Kaplan-Meier method.

11.4.1. Participant Disposition

The number and percentage of participants screened and randomized and the primary reasons for screening failure and discontinuation will be summarized.

11.4.2. Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment arm.

11.4.3. Efficacy Analyses

11.4.3.1. Primary Efficacy Analysis

The primary endpoint of CR30 rate at the week 120 assessment per independent central review according to the Lugano Classification will be analyzed by the Cochran-Mantel–Haenszel (CMH) test using the following stratification factors:

- Follicular Lymphoma International Prognostic Index (FLIPI) score (0 or 1 [low risk] vs. 2 [intermediate risk] vs. 3 to 5 [high risk])

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- Longest lesion diameter (≤6 cm vs. >6 cm)

An associated odds ratio and its 95% CI will be estimated. CR30 rate with the corresponding 95% exact CI will be calculated by the Clopper-Pearson method for each treatment arm.

The primary analysis of CR30 will be performed after all randomized participants in Part 2 complete 30-month tumor assessments or discontinue the study.

The subgroup analysis of CR30 rate will be conducted using a similar approach within each subgroup. Subgroup analyses will be performed for the primary endpoint of CR30. These analyses may include the following subgroups:

- Age (<65 vs ≥65)
- ECOG (0 vs 1-2)
- Baseline FLIPI (low risk [0-1] vs intermediate risk [2] vs high risk [3-5])
- Longest lesion diameter (≤6 cm vs >6 cm)
- Region (US vs non-US)
- Disease stage by Lugano Classification (1-2 vs 3-4)

11.4.3.2. Key Secondary Efficacy Analysis

PFS and EFS, assessed by independent central review according to the Lugano Classification and OS, will be analyzed. The HR and its 95% CI will be estimated by a stratified Cox regression model with the same stratification factors used in analysis of the CR30 rate. The median time and its 95% CI will be calculated using the Kaplan-Meier method for each treatment arm.

CR30 rate at the week 120 assessment by local investigator, according to the Lugano Classification, will be analyzed using the same method as the primary analysis (see Section 11.4.3.1).

Change from baseline of EORTC-QLQ-C30 physical functioning will be analyzed using the Mixed-Effect Model Repeated Measure (MMRM) model.

11.4.3.3. Secondary Efficacy Analysis

ORR at EOI and at EOS assessed by independent central review and by local investigator review according to Lugano Classification will be analyzed using the CMH test. An associated odds ratio and 95% CI will be calculated. ORR with the corresponding 95% exact CI will be calculated by the Clopper-Pearson method for each treatment arm.

DOR, assessed by independent central review and by local investigator review; PFS and EFS, assessed by local investigator review according to Lugano Classification; TTNT, and OS will be analyzed. The HR and its 95% CI will be estimated by a stratified Cox regression model with the same stratification factors used in analysis of CR30 rate. The median time and its 95% CI will be calculated using the Kaplan-Meier method for each treatment arm.

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11.4.4. Control of Multiplicity

The multiplicity is controlled at 2-sided α 0.05 level. A hierarchical testing procedure will be used to adjust for multiple statistical testing of the primary and key secondary efficacy endpoints.

1. First, the primary efficacy endpoint, CR30 per independent central review, will be compared between the two treatment arms. If it is statistically significant, the further testing will be performed per Step 2. Otherwise, the following key secondary endpoints will not be compared.
2. The PFS per independent central review will be compared between the two treatment arms. If it is statistically significant, the further testing will be performed per Step 3. Otherwise, the following key secondary endpoints will not be compared.
3. The EFS per independent central review will be compared between the two treatment arms. If it is statistically significant, the further testing will be performed per Step 4. Otherwise, the following endpoint will not be compared.
4. The change from baseline in physical functioning (EORTC-QLQ-C30) will be compared between the two treatment arms using the MMRM model. If it is statistically significant, then further testing will be performed per Step 5. Otherwise, the following key secondary endpoints will not be compared.
5. The OS will be compared between the two treatment arms.

The alpha spending for each endpoint at its interim and final analyses will depend on the number of interim analyses, the alpha spent at the previous interim and the remaining alpha. The alpha control for interim and final analyses of the key secondary endpoints PFS, EFS, and OS is described in Section 11.5.

The final choice for hierarchy of endpoints, multiple testing approach, and interim analysis details (including final choice of spending function) will be provided in the SAP.

11.4.5. Safety Analysis

11.4.5.1. Adverse Events

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Definitions

For safety variables, 3 observation periods are defined:

- The pretreatment period is defined as the time from signing the ICF to before the first dose of study drug.
- The on-treatment period is defined as the day from first dose of study drug to the last dose of study drug plus 90 days or until the start of next non-protocol anti-lymphoma therapy, whichever is earlier.
- The post-treatment period is defined as the time after the on-treatment period.

Analysis

All AEs reported in this study will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA®).

Summaries of all TEAEs by treatment group will include:

- The number (n) and percentage (%) of participants with at least 1 TEAE by SOC and PT
- TEAEs by severity (according to the grading scale outlined in Section 10.3.4), presented by SOC and PT
- TEAEs related to treatment, presented by SOC and PT
- Treatment-emergent AESIs (defined with a PT or a prespecified grouping)
- Treatment-emergent adverse events leading to permanent treatment discontinuation

Deaths and other SAEs will be summarized by treatment group.

11.4.5.2. Other Safety

Vital Signs

Vital signs (temperature, pulse, blood pressure, and respiration rate) will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

Laboratory Tests

Laboratory test results will be summarized by treatment group.

Shift tables may be used to present the results for laboratory tests of interest.

11.4.5.3. Treatment Exposure

The extent of exposure to the investigational drug (characterized according to the number of participants exposed, the duration of exposure, and the dose to which they were exposed) will be summarized.

11.4.5.4. Treatment Compliance

Treatment compliance will be summarized. The details will be defined in the SAP.

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11.4.6. Pharmacokinetics

11.4.6.1. Analysis of Drug Concentration Data

Odronextamab concentrations in serum over time will be measured.

PK parameters of odronextamab including pre-dose and EOI concentrations will be generated and summarized with descriptive statistics.

11.4.7. Analysis of Immunogenicity Data

Immunogenicity will be characterized by the ADA and NAb responses observed:

- ADA Negative, defined as ADA-negative response in the ADA assay at all timepoints, regardless of any missing samples
- Pre-existing immunoreactivity, defined as a positive ADA assay response at baseline with all post-dose ADA results negative or a positive assay response at baseline with all post-dose ADA assay responses less than 9-fold over baseline titer levels
- Treatment-emergent ADA response, defined as any post-dose positive ADA assay response when the baseline results are negative or missing
  - Treatment-emergent ADA response may be further characterized as persistent, transient, or indeterminate
- Treatment boosted ADA response, defined as any post-dose positive ADA assay response that is 9-fold over baseline titer levels when baseline is positive in the ADA assay
- Titer Categories (Maximum Titer Values):
  - Low (titer < 1,000)
  - Moderate (1,000 ≤ titer ≤ 10,000)
  - High (titer >10,000)
- NAb status for samples that are positive in the ADA assay

Incidence of treatment-emergent ADA and NAb will be assessed as absolute occurrence (N) and percentage of participants (%), grouped by study cohorts and ADA titer level.

Plots of drug concentrations will be examined, and the influence of ADAs and NAbs on individual PK profiles may be evaluated. Assessment of impact of ADA and NAbs on safety and efficacy may be provided.

11.4.8. Analysis of Pharmacodynamic and Exploratory Biomarker Data

Pharmacodynamic analyses may be conducted on exploratory biomarkers, as appropriate.

Biomarker analyses will be summarized in a separate report. Detailed description of statistical methods that will be used for biomarker data analyses will be provided in a separate Biomarker Analytical Plan.

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11.4.9. Analysis of Quality of Life Data

PRO data will be summarized and analyzed for Part 2 (Randomized Phase). PRO instruments will be scored according to their respective validation papers, scoring algorithms, and user's guides. PRO compliance rates will be summarized by visit. Summary statistics of absolute scores and change from baseline by visit will be reported for each scale/item of EORTC-QLQ-C30, FACT-LymS, FACT-G GP5, and EQ-5D-5L index and EQ VAS. Line charts depicting the mean and mean change from baseline will be provided. Summary statistics by visit for PGIS and PGIC will also be reported.

Change from baseline of scales/items will be analyzed using the MMRM model.

Time to deterioration (TTD) across scales/items will be summarized using Kaplan-Meier method. The hazard ratio and its 95% confidence interval will be estimated by a stratified Cox proportional hazard model.

Detailed description of statistical methods for PRO analyses will be outlined in a separate PRO Analytical Plan.

11.5. Interim Analysis

An interim futility assessment for CR30 is planned for Part 2 in this study when 100 randomized participants (i.e, 50 per arm) complete their 6-month tumor assessment or discontinue the study, whichever is earlier. The futility rule will be based on the observed CR rate (ie, CR6 rate) and ORR at 6 months. The futility rule is:

- Observed CR6 in odronextamab arm / Observed CR6 in rituximab-chemotherapy arm < 0.85

and

- Observed ORR6 in odronextamab arm / Observed ORR6 in rituximab-chemotherapy arm < 0.9

The proposed futility boundary is non-binding. The results of the futility assessment will be reviewed by the IDMC to make recommendation of go/no go. There is no plan to claim efficacy superiority based on the interim results and no CR30 in any patients will be observed at the time; therefore, no Type I error rate adjustment is needed at this look.

At the time of primary analysis of CR30 in Part 2 (randomized portion), approximately 92 PFS events (53% of total events) are expected. While descriptive analysis of PFS and EFS will be performed at this time, no decision regarding futility or superiority will be made at the time. However, 2-sided alpha of 0.0001 will be spent to control the FWER and maintain integrity of the analysis of PFS.

After the primary analysis of CR30, one formal interim efficacy analysis of PFS is planned using a Lan-DeMets (O'Brien-Fleming) spending function, when approximately 130 PFS events (75% of total events) are observed.

A formal interim efficacy analysis of EFS will also be performed at the time of the PFS interim efficacy analysis.

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If the comparison is significant for CR30 at the primary analysis, the PFS will be compared at the planned interim analysis. If the PFS is not significant, the comparison of PFS will continue to its final efficacy analysis.

If the interim efficacy analysis of PFS is significant, EFS will be compared. If EFS is not significant, the comparison of EFS will continue to its final efficacy analysis.

If CR30, PFS, EFS, and change from baseline in physical functioning are all significant, OS will be compared at the end of study.

Table 30 summarizes the alpha spending for interim and final efficacy analyses based on the planned number of PFS events. The actual alpha spending at the interim efficacy analyses will be determined by the O'Brien-Fleming spending function based on the actual number of PFS events observed at the time of interim efficacy and planned number of PFS events for the final analyses. The final nominal alpha will be based on the actual number of PFS events observed at the time of interim efficacy and final analyses.

Table 30: Alpha Spending in Group Sequential Design Using Lan-DeMets (O'Brien-Fleming) Spending Function for PFS

Endpoint	Interim Efficacy Analysis		Final Efficacy Analysis	
	No. Events Needed	2-Sided Nominal α	No. Events Needed	2-Sided Nominal α
PFS	130 (75.1%)	0.019388	173 (100%)	0.04412

The alpha spending for interim and final analyses of EFS will be specified in the SAP.

Three interim analyses of OS will be performed at the time of the primary analysis of CR30, the interim analysis of PFS, and the final analyses of PFS. The potential for harm, i.e., the probability of the HR for OS exceeding 1, will be accessed at each interim analysis of OS. These looks are expected to coincide with approximately 45%, 65%, and 90% information fraction for OS (Table 31). At each of these interim looks at OS, 2-sided alpha of 0.0001 will be spent. Assessment of the potential for harm at interim timepoints for OS will be based on the conditional probability of observing a numerically favorable HR given interim results. Specifically, if Prob (Final HR<1 | observed interim data) < 20% under the null trend, a potential for harm cannot be excluded. This boundary is non-binding. Under the null hypothesis (HR=1, i.e., equipoise with respect to OS), Table 32 provides the hazard ratio boundaries corresponding to this conditional probability criterion, and the probability of stopping at each look under various true hazard ratios (e.g., HR=0.55, 0.85, 1, 1.25, 1.5).

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Table 31: Number of Events and Information Fractions (IF*) at Each Look

HR	1st look at 47 months	2nd look at 68 months	3rd look at 95 months	Final look at 106 months
0.55	21 (44.7%)	31 (66.0%)	43 (91.5%)	47
0.85	24 (42.9%)	37 (66.1%)	51 (91.1%)	56
1	27 (44.3%)	40 (65.6%)	55 (90.2%)	61
1.25	30 (44.1%)	44 (64.7%)	61 (89.7%)	68
1.5	33 (44.6%)	49 (66.2%)	67 (90.5%)	74

IF=information fraction
* IF was based on the total number events at 106 months.

Table 32: Operating Characteristics of Prob (HR<1 Observed Data) <20% for Assessing the Potential for Harm in OS

True HR	Probability of stopping at 1st look (HR boundary=1.443)	Cumulative probability of stopping at 2nd look (HR boundary=1.217)	Cumulative probability of stopping at 3rd look (HR boundary=1.079)	Probability (Final HR* ≥1)
0.55	3.4%	5%	5.4%	0.6%
0.85	12.7%	20.2%	28.2%	6.1%
1	21%	33.4%	47.7%	9.0%
1.25	37.3%	59.2%	76.4%	6.2%
1.5	56.1%	78.4%	91.8%	3.5%

HR=hazard ratio; OS=overall survival; Prob=probability
* Final HR refers to the HR observed at 106 months if OS follow-up continues beyond the 3rd look.

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12. QUALITY CONTROL AND QUALITY ASSURANCE

In accordance with ICH E6, the sponsor is responsible for quality assurance to ensure that the study is conducted and the data generated, recorded, and reported in compliance with the protocol, GCP, and any applicable regulatory requirement(s). The planned quality assurance and quality control procedures for the study are described in this section.

12.1. Data Management and Electronic Systems

12.1.1. Data Management

A data management plan specifying all relevant aspects of data processing for the study (including data validation [quality-checking], cleaning, correcting, and releasing) will be maintained and stored at Regeneron (Sponsor).

Adverse events and medical history will be coded using MedDRA. A medical coding plan will specify the processes and the dictionary used for coding. All data coding (eg, AEs, baseline findings, medication, relevant medical history, and surgical history/oncologic history) will be done using internationally recognized and accepted dictionaries.

The CRF data for this study will be collected with an electronic data capture (EDC) system.

12.1.2. Electronic Systems

Electronic systems that may be used to process and/or collect data in this study will include the following:

- IVRS/IWRS system – randomization, study drug supply
- EDC system – data capture (Medidata Rave)
- Statistical Analysis System (SAS) – statistical review and analysis
- Pharmacovigilance safety database
- Central imaging
- eCOA – patient reported outcomes

12.2. Study Monitoring

12.2.1. Monitoring of Study Sites

Regeneron uses a study-specific risk-based approach to study monitoring and oversight, aligned with risk-based quality principles, outlined in ICH E6 (R2) Guideline for GCP. Risk-Based Quality Monitoring (RBQM) methodology focuses on employing a fit-for-purpose monitoring strategy, supported either directly by Regeneron as sponsor, or via our CRO partners. RBQM strategies include: reduced source data verification (SDV), targeted source data review (SDR), the use of off-site/remote and triggered on-site monitoring visits, and centralized monitoring to identify site level risks and study level trends. The investigator must allow study-related monitoring activities to occur.

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The study monitors will perform ongoing SDR to verify that data recorded in the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the current approved protocol version and any other study agreements, ICH GCP, and all applicable regulatory requirements.

12.2.2. Source Document Requirements

Investigators are required to prepare and maintain adequate and accurate participant records (source documents). The site is responsible to ensure quality within their records and systems and are accountable for ensuring that all source data and CRF data are timely, accurate and complete.

The investigator must keep all source documents on file with the CRF (throughout this protocol, CRF refers to either a paper CRF or an electronic CRF). Case report forms and source documents must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

12.2.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on eCRFs within the EDC system by trained site personnel. All required CRFs must be completed for each and every participant enrolled in the study. The investigator must ensure the accuracy, completeness, and timeliness of the data reported to the sponsor in the CRFs. After review of the clinical data for each participant, the investigator must provide an electronic signature. A copy of each participant's CRF casebook is to be retained by the investigator as part of the study record and must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

Corrections to the CRF will be entered in the CRF by the investigator or an authorized designee. All changes, including date and person performing corrections, will be available via the audit trail, which is part of the EDC system. For corrections made via data queries, a reason for any alteration must be provided.

12.3. Audits and Inspections

This study may be subject to a quality assurance audit or inspection by the sponsor or regulatory authorities. Should this occur, the investigator is responsible for:

- Informing the sponsor of a planned inspection by the authorities as soon as notification is received and authorizing the sponsor's participation in the inspection
- Providing access to all necessary facilities, study data, and documents for the inspection or audit
- Communicating any information arising from inspection by the regulatory authorities to the sponsor immediately
- Taking all appropriate measures requested by the sponsor to resolve the problems found during the audit or inspection

Documents subject to audit or inspection include but are not limited to all source documents, CRFs, medical records, correspondence, ICFs, IRB/EC files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting

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pharmacy facilities. Conditions of study material storage are also subject to inspection. In addition, representatives of the sponsor may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the investigator's institution.

In all instances, the confidentiality of the data must be respected.

12.4. Study Documentation

12.4.1. Certification of Accuracy of Data

A declaration assuring the accuracy and content of the data recorded on the eCRF must be signed electronically by the investigator. This signed declaration accompanies each set of a participant's final eCRF that will be provided to the sponsor.

12.4.2. Retention of Records

The investigator must retain all essential study documents, including ICFs, source documents, investigator copies of CRFs, and drug accountability records for at least 15 years following the completion or discontinuation of the study or longer, if a longer period is required by relevant regulatory authorities. *Note: under EU CTR, the sponsor should archive the content of the Clinical Trial Master File for at least 25 years after the end of the clinical trial, unless other Union law requires archiving for longer*. The investigator must obtain written approval from the sponsor before discarding or destroying any essential study documents during the retention period following study completion or discontinuation. Records must be destroyed in a manner that ensures confidentiality.

If the investigator's personal situation is such that archiving can no longer be ensured, the investigator must inform the sponsor (written notification), and the relevant records will be transferred to a mutually agreed-upon destination.

12.4.3. Recruitment Strategy

Potential study participants may be identified by the investigator through a variety of means, such as publicizing the trial or using existing patient lists. Recruitment resources may include but are not limited to recruitment flyers, brochures, social media ads, newspaper ads, radio ads, etc. A third-party vendor may assist in recruitment efforts, such as the development of recruitment materials. All patient-facing recruitment material, including media advertising and receptionist scripts, will be reviewed and approved by the appropriate IRB/EC/authority prior to use. Resources may be in paper or electronic form. Regeneron will not access any patient-identifiable information as part of recruitment efforts.

12.4.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.
- The participant must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure

must also be explained to the participant, who will be required to give consent for their data to be used as described in the ICF.

- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The contract between sponsor and study sites specifies responsibilities of the parties related to data protection, including handling of data security breaches and respective communication and cooperation of the parties.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

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13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice Statement

It is the responsibility of both the sponsor and the investigator(s) to ensure that this clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the ICH guidelines for GCP and applicable regulatory requirements.

13.2. Informed Consent

The principles of informed consent are described in ICH guidelines for GCP.

The ICF used by the investigator must be reviewed and approved by the sponsor prior to submission to the appropriate IRB/EC. A copy of the IRB/EC-approved ICF and documentation of approval must be provided to the sponsor before study drug will be shipped to the study site.

It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain written informed consent from each participant prior to his/her participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the participant in language that he/she can understand. The ICF should be signed and dated by the participant and by the investigator or authorized designee who reviewed the ICF with the participant.

- Participants who can write but cannot read will have the ICF read to them before signing and dating the ICF together with the impartial witness and the investigator or authorized designee.
- Participants who can understand but who can neither write nor read will have the ICF read to them in the presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

The original ICF must be retained by the investigator as part of the participant's study record, and a copy of the signed ICF must be given to the participant.

If new safety information results in significant changes in the risk-benefit assessment, or if there are significant changes to the study procedures, the ICF must be reviewed and updated appropriately. All study participants must be informed of the new information and provide their written consent if they wish to continue in the study. The original signed revised ICF must be maintained in the participant's study record, and a copy must be given to the participant.

13.3. Participants' Confidentiality and Data Protection

The investigator must take all appropriate measures to ensure that the anonymity of each study participant will be maintained. Participants should be identified by a participant identification number only on CRFs or other documents submitted to the sponsor. Documents that will not be submitted to the sponsor (eg, signed ICF) must be kept in strict confidence.

The participant's and investigator's personal data, which may be included in the sponsor database, will be treated in compliance with all applicable laws and regulations. The sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

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13.4. Institutional Review Board/Ethics Committee

An appropriately constituted IRB/EC, as described in ICH guidelines for GCP, must review and approve:

- The protocol, ICF, and any other materials to be provided to the participants (eg, advertising) before any participants may be enrolled in the study
- Any amendment or modification to the study protocol or ICF before implementation, unless the change is necessary to eliminate an immediate hazard to the patient, in which case the IRB/EC should be informed as soon as possible
- Ongoing studies on an annual basis or at intervals appropriate to the degree of risk

In addition, the IRB/EC should be informed of any event likely to affect the safety of participants or the continued conduct of the clinical study.

A copy of the IRB/EC approval letter with a current list of the IRB/EC members and their functions must be received by the sponsor prior to shipment of drug supplies to the investigator. The approval letter should include the study number and title, the documents reviewed, and the date of the review.

Records of the IRB/EC review and approval of all study documents (including approval of ongoing studies) must be kept on file by the investigator.

13.5. Clinical Study Data Transparency

Final study results will be published on public clinical trial registries according to applicable local guidelines and regulations. For data integrity, scientific, and statistical reasons, published results from all participants will be disclosed following EOS (Section 6.1.4).

Treatment codes will be disseminated to each investigation site thereafter.

For purposes of data disclosure, interim analyses will be available for disclosure when required by local regulations. If the integrity of the ongoing study cannot be ensured, then only final results will be disclosed.

14. PROTOCOL AMENDMENTS

The sponsor may not implement a change in the design of the protocol or ICF without an IRB/EC-approved amendment. Where required per local legislation, regulatory authority approval will also be sought.

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15. PREMATURE TERMINATION OF THE STUDY OR CLOSEOUT OF A SITE

15.1. Premature Termination of the Study

The sponsor has the right to terminate the study prematurely. Reasons may include efficacy, safety, or futility, among others. Should the sponsor decide to terminate the study, the investigator(s) will be notified in writing.

15.2. Close-out of a Site

The sponsor and the investigator have the right to close-out a site prematurely.

Investigator's Decision

The investigator must notify the sponsor of a desire to close-out a site in writing, providing at least 30 days' notice. The final decision should be made through mutual agreement with the sponsor. Both parties will arrange the close-out procedures after review and consultation.

Sponsor's Decision

The sponsor will notify the investigator(s) of a decision to close-out a study site in writing. Reasons may include the following, among others:

- The investigator has received all items and information necessary to perform the study, but has not enrolled any participant within a reasonable period of time
- The investigator has violated any fundamental obligation in the study agreement, including but not limited to, breach of this protocol (and any applicable amendments), breach of the applicable laws and regulations, or breach of any applicable ICH guidelines
- The total number of participants required for the study are enrolled earlier than expected

In all cases, the appropriate IRB/EC and Health Authorities must be informed according to applicable regulatory requirements, and adequate consideration must be given to the protection of the participants' interests.

16. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

17. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

18. PUBLICATION POLICY

Publication rights and procedures will be outlined in a separate clinical study agreement.

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20. INVESTIGATOR'S AGREEMENT

I have read the attached protocol, A Phase 3, Open-label, Randomized Study to Compare the Efficacy and Safety of Odronextamab (REGN1979), an Anti-CD20 x Anti-CD3 Bispecific Antibody, Versus Investigator's Choice in Previously Untreated Participants with Follicular Lymphoma (OLYMPIA-1) and agree to abide by all provisions set forth therein.

I agree to comply with the current ICH Guideline for GCP and the laws, rules, regulations, and guidelines of the community, country, state, or locality relating to the conduct of the clinical study.

I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the sponsor or a partnership in which the sponsor is involved. I will immediately disclose it in writing to the sponsor if any person who is involved in the study is debarred or if any proceeding for debarment is pending, or, to the best of my knowledge, threatened.

This document contains confidential information of the sponsor, which must not be disclosed to anyone other than the recipient study staff and members of the IRB/EC. I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

_____ _____

(Signature of Investigator) (Date)

_____

(Printed Name)

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APPENDIX 1. MALIGNANT LYMPHOMA RESPONSE DEFINITIONS PER LUGANO CRITERIA

For CT/MRI-based response, up to 6 of the largest nodal and extranodal lesions that are measurable in 2 diameters (longest diameter [LDi] and shortest diameter) should be selected as target lesions from different body regions representative of the patient's overall disease burden and include mediastinal and retroperitoneal disease, if involved. A measurable nodal lesion must have an LDi > 1.5 cm. A measurable extranodal lesion must have an LDi > 1.0 cm. All other disease consistent with lymphoma but not selected as target lesions (including nodal, extra nodal, and assessable disease) should be followed as non-measurable disease. All areas of disease should be evaluated at each tumor assessment timepoint as per the Lugano criteria (Cheson, 2014a).

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS†	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable

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No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions

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SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS

(Medical/Study Director, Regulatory Representative, Clinical Study Lead, and Biostatistician)

To the best of my knowledge, this report accurately describes the planned conduct of the study.

Study Title: A Phase 3, Open-label, Randomized Study to Compare the Efficacy and Safety of Odronextamab (REGN1979), an Anti-CD20 x Anti-CD3 Bispecific Antibody, Versus Investigator's Choice in Previously Untreated Participants with Follicular Lymphoma (OLYMPIA-1)

Protocol Number: R1979-HM-2298

Protocol Version: R1979-HM-2298 Amendment 1

See appended electronic signature page

Sponsor's Responsible Medical/Study Director

See appended electronic signature page

Sponsor's Responsible Regulatory Liaison

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Sponsor's Responsible Clinical Study Lead

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Sponsor's Responsible Biostatistician

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