Protocol

Protocol title:
HERMES: Effects of ziltivekimab versus placebo on morbidity and mortality in patients with heart failure with mildly reduced or preserved ejection fraction and systemic inflammation.

Short title:
HERMES – A research study to look at how ziltivekimab works compared to placebo in people with heart failure and inflammation.

Substance name: Ziltivekimab

Protocol version number: 4.0

Protocol version applicability: Local version for United Kingdom

Universal Trial Number: U1111-1280-0810

EU CT number: 2022-501939-16-00

IND Number: 161856

Study phase: 3

In the following, Novo Nordisk A/S and its affiliates will be stated as “Novo Nordisk”.

Protocol amendment summary of changes table

DOCUMENT HISTORY		
Document version	Date	Applicable in country(-ies) and/or site(s)
4.0	18 July 2023	United Kingdom
3.0	03 April 2023	All
2.0	07 February 2023	Argentina, Japan, South Korea
1.0	11 October 2022	All

Protocol version 4.0 (18 July 2023)

This amendment is considered to be non-substantial for all countries based on the criteria set forth in Article 2(13) of Regulation (EU) No 536/2014 of the European Parliament and the Council of 16 April 2014;[1] because it neither substantially impacts the safety or rights of the participants nor the reliability or robustness of the data generated in the study.

Overall rationale for preparing protocol, version 4.0:

Document has been revised to update country/region-specific requirements for United Kingdom.

Deleted text is written as ~~strikethrough~~ and new text *italic*.

Section # and name	Description of change	Rationale
Section 10.11.45 Appendix 11: Country-specific requirements for United Kingdom.	Text modified: Section 5.2, exclusion criterion #3 and Appendix 4 (Section 10.4.2): Contraceptive measures considered adequate include highly effective contraceptive methods in accordance with the CTFG (Clinical Trial Facilitation Group): Recommendations related to contraception and pregnancy testing in clinical studies.[68] ~~This means use of double barrier methods is not applicable for United Kingdom.~~ *The use of double barrier method is not acceptable for United Kingdom as the sole means of contraception but may be used as a form of additional contraception in addition to the highly effective methods listed in Table 10-3.*	To provide additional clarification regarding the use of double barrier method as per local requirements in UK.

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1 Protocol summary

1.1 Synopsis

Overall design

This is an interventional, randomised, parallel-group, double-blind, placebo-controlled, multi-centre, multi-national cardiovascular outcomes trial (CVOT) designed to evaluate the effects of ziltivekimab 15 mg versus placebo (randomised 1:1), both administered s.c. once-monthly and added to standard of care, on morbidity and mortality of participants with heart failure (HF) with mildly reduced ejection fraction (HFmrEF) or HF with preserved ejection fraction (HFpEF) and systemic inflammation.

The study consists of 3 periods: a screening period (up to 5 weeks), a treatment period and a 3-month follow-up period after the end of treatment visit. Eligible participants will be randomly assigned to study intervention prior to initiation of the treatment period. The total study duration for an individual participant is estimated to be up to 4 years, depending on when the participant is enrolled.

Efficacy and safety data will be collected at regular intervals throughout the study.

Rationale

Heart failure (HF) affects approximately 2% of the adult population in developed countries and approximately 64.3 million patients worldwide.[2-4] Despite optimal management, most patients with HF have troublesome symptoms, including dyspnoea and fatigue. HF causes substantial mortality and morbidity and has major effects on physical function and quality of life.[5, 6]

The diagnosis of HF is currently classified based on left ventricular ejection fraction (LVEF). The primary phenotypes of chronic heart failure (CHF) are HF with reduced ejection fraction (HFrEF) (LVEF ≤40%), HF with mildly reduced ejection fraction (HFmrEF) (LVEF of 41-49%) and HF with preserved ejection fraction (HFpEF) (LVEF ≥50%).[2, 3] HFmrEF and HFpEF represents approximately half of HF cases[7] and the proportion being classified as HFpEF has increased the last decade.[8] Several pathophysiological pathways have been proposed linking systemic inflammation to the development and worsening of HFmrEF and HFpEF.[8] No randomised controlled trials have been conducted investigating interleukin 6 (IL-6) inhibition in the HFmrEF and HFpEF population.

Ziltivekimab is a human monoclonal antibody directed against the IL-6.[9] Ziltivekimab once-monthly has been shown to reduce inflammation as measured by high-sensitivity C-reactive protein (hs-CRP)[9], in patients with chronic kidney disease (CKD) and systemic inflammation. Thereby, ziltivekimab has the potential to reduce inflammation in HFmrEF and HFpEF and consequently may reduce symptoms, as well as long-term morbidity and mortality. The aim of the current study is to demonstrate the efficacy of ziltivekimab in reducing morbidity and mortality in patients with HFmrEF or HFpEF and systemic inflammation.

Objectives, endpoints and estimand

The objectives and confirmatory endpoints included in the test hierarchy are summarised in the table below.

The primary clinical question is: What is the treatment effect of ziltivekimab 15 mg s.c. once-monthly vs placebo, both added to standard of care, on time to first occurrence of either CV death or HF hospitalisation or urgent HF visit for patients with HFmrEF or HFpEF and systemic inflammation, irrespective of treatment discontinuation or treatment pauses for any reason, changes to CV risk lowering background medication, coronary revascularisation, or device implantation while the patient is alive (i.e., have not had a non-CV death)?

Objectives	**Endpoints**		
Primary	**Title**	**Time frame**	**Unit**
To demonstrate the superiority of ziltivekimab 15 mg s.c. once-monthly versus placebo, both added to standard of care, in reducing the risk of CV death and HF events in participants with HFmrEF or HFpEF and systemic inflammation.	*Primary*		
	Time to first occurrence of a composite HF endpoint consisting of: • CV death • HF hospitalisation or urgent HF visit	From randomisation (month 0) to end of study (up to 48 months)	Months
Secondary	**Title**	**Time frame**	**Unit**
To demonstrate the superiority of ziltivekimab 15 mg s.c. once-monthly versus placebo, both added to standard of care, in reducing the risk of expanded composite HF endpoint in participants with HFmrEF or HFpEF and systemic inflammation.	*Confirmatory secondary*		
	Time to first occurrence of 4-point expanded composite HF endpoint, a composite endpoint consisting of: • CV death • HF hospitalisation or urgent HF visit • Non-fatal MI • Non-fatal stroke	From randomisation (month 0) to end of study (up to 48 months)	Months
See primary objective	Number of CV deaths, HF hospitalisations or urgent HF visits (first and recurrent)	From randomisation (month 0) to end of study (up to 48 months)	Count of event
To demonstrate the superiority of ziltivekimab 15 mg s.c. once-monthly versus placebo, both added to standard of care, in reducing the risk of death in participants with HFmrEF or HFpEF and systemic inflammation.	Time to occurrence of CV death	From randomisation (month 0) to end of study (up to 48 months)	Months
	Time to occurrence of all-cause death	From randomisation (month 0) to end of study (up to 48 months)	Months

Abbreviations: CV = cardiovascular; HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; MI = myocardial infarction; s.c. = subcutaneous.

Study intervention groups and duration

The following study interventions will be supplied by Novo Nordisk A/S:

- ziltivekimab 15 mg/mL single-use prefilled syringe (1 mL).
- placebo single-use prefilled syringe (1 mL).

The study is event driven; therefore, end of study will be scheduled according to projected study closure. Study duration is expected to be up to 4 years following randomisation of the first participant. Hence, the total study duration for an individual participant is estimated to be up to 4 years, depending on when the participant is enrolled.

Number of participants

Approximately 5,600 participants will be randomly assigned to study intervention (1:1 to ziltivekimab or placebo).

Participant characteristics

Key inclusion and exclusion criteria are summarised below:

Key inclusion criteria

- Serum hs-CRP ≥2 mg/L at screening (visit 1)[a]

Disease specific - cardiovascular

- At least one of the following[a]:
    a. NT-proBNP ≥ 300 pg/mL at screening (Visit 1) for patients without ongoing atrial fibrillation/flutter. If ongoing atrial fibrillation/flutter at screening (visit 1), NT-proBNP must be ≥600 pg/mL.
    b. Hospitalisation or urgent/unplanned visit with a primary diagnosis of decompensated heart failure which required intravenous loop diuretic treatment, within the last 9 months prior to screening (visit 1) *in combination with* NT-proBNP ≥ 200 pg/mL at screening (Visit 1) for patients without ongoing atrial fibrillation/flutter. If ongoing atrial fibrillation/flutter at screening (visit 1), NT-proBNP must be ≥600 pg/mL.
- Diagnosis of heart failure (NYHA Class II-IV).
- LVEF > 40% documented by echocardiography within 12 months prior to or at screening (visit 1). The LVEF must be documented in medical records and the most recent measurement must be used to determine eligibility with no interim event signalling potential deterioration in ejection fraction (e.g., MI or HF hospitalisation).
- Structural heart disease *and/or* functional heart disease documented by echocardiography within 12 months prior to or at screening (visit 1) showing at least one of the following:
- LA volume index > 34 mL/m^2.
- LA diameter ≥ 3.8 cm.
- LA length ≥ 5.0 cm.
- LA area ≥ 20 cm^2.
- LA volume ≥ 55 mL.
- Intraventricular septal thickness ≥1.1 cm.
- Posterior wall thickness ≥1.1 cm.
- LV mass index ≥115 g⁄m^2 in men or ≥ 95 g⁄m^2 in women.
- E/e' (mean septal and lateral) ≥ 10.
- e' (mean septal and lateral) < 9 cm/s.
- No heart failure hospitalisations or urgent heart failure visits between screening (visit 1) and randomisation (visit 2).

[a] Patients participating in the prevalence study (NN6018-7527) may be enrolled based on the hs-CRP and/or NT-proBNP (requiring corresponding ECG from the same date) results obtained in the study, if no more than 90 days old.

Key exclusion criteria

Medical conditions – cardiovascular

- Myocardial infarction, stroke, unstable angina pectoris, transient ischaemic attack, or heart failure hospitalisation, within 30 days prior to screening (visit 1).
- Systolic blood pressure ≥180 mmHg at screening (visit 1). If the systolic blood pressure is 160-179 mmHg, the patient should be receiving ≥3 antihypertensive drugs. *(Note: Potential participants may be retested for this criterion within the visit window and without rescreening, at the discretion of the investigator*).
- Heart rate above 110 or below 40 beats per minute as evaluated on the ECG performed at screening (visit 1) *(Note: Potential participants may be retested for this criterion within the visit window and without rescreening, at the discretion of the investigator).*
- Planned coronary, carotid or peripheral artery revascularisation known during the screening period (visit 1). (*Note: Planned coronary angiogram is not exclusionary)*.
- Planned cardiac device or atrial flutter/atrial fibrillation ablation procedure known during the screening period (visit 1).
- Major cardiac surgical, non-cardiac surgical, or major endoscopic procedure (thoracoscopic or laparoscopic) within the past 60 days prior to randomisation (visit 2) or any major surgical procedure planned at the time of randomisation (visit 2).
- Heart failure due to infiltrative cardiomyopathy (e.g., sarcoid, amyloid), arrhythmogenic right ventricular cardiomyopathy, Takutsubo cardiomyopathy, genetic hypertrophic cardiomyopathy or obstructive cardiomyopathy, active myocarditis, constrictive pericarditis, cardiac tamponade, uncorrected more than moderate primary valve disease.
- Primary pulmonary hypertension, chronic pulmonary embolism, severe pulmonary disease including COPD.
- Any other condition judged by the investigator that could account for heart failure symptoms and signs (e.g., anaemia, hypothyroidism).

Medical conditions – infections/immunosuppression

- Clinical evidence of, or suspicion of, active infection at the discretion of the investigator.

Data monitoring committee

Yes

1.2 Flowchart

Procedure/period	Protocol section	Screening period[a]	Randomisation	Intervention/Treatment period (event driven)										EoT	EoS
				First year						Remaining years					
Visit		V1	V2	V3	P4[b]	V5	V6	V7	V8	P9[b], P11[b], P13[b], P15[b], P17[b]	V10, V14, V18[c]	V12	V16	V-EoT	V-EoS
Timing of visit (months unless otherwise specified)		Up to - 5 wks[d]	0	1	2	3	6	9	12	15, 21, 27, 33, 39	18, 30, 42	24	36	EoT	EoT+ 3 mos
Visit window (days)				±3	±3	±3	±7	±7	±7	±10	±10	±10	±10		+10
PARTICIPANT RELATED INFO/ ASSESSMENTS															
Informed consent	10.1.3	X													
Demography[e]	8.9	X													
Eligibility criteria	5.1 5.2	X	X												
Randomisation	6.3		X												
Concomitant therapy	6.8	X[f]	X	X	X	X	X	X	X	X	X	X	X	X	X
Discontinuation criteria	7.1.1			X	X	X	X	X	X	X	X	X	X		
Medical history/concomitant illness incl. COVID-19	8.2.5	X[f]	X												
Infection serology including hepatitis B virus DNA monitoring[g]	8.2.4, 8.2.8	X[g]		X[g]		X[g]	X[g]	X[g]	X[g]		X[g]	X[g]	X[g]	X[g]	X
Tuberculosis screening	8.2.7	X													
Childbearing potential	8.9	X													
Urine pregnancy test[h]	8.2.9	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Tobacco and nicotine products use	8.10		X											X	
CLINICAL OUTCOME ASSESSMENTS															
ECG	8.2.3.1	X[a,i]	X			X			X					X	
Echocardiography	8.2.3.2	X[j]													
Kansas City Cardiomyopathy Questionnaire (KCCQ)[k]	8.1.2.1		X				X		X						

Procedure/period	Protocol section	Screening period[a]	Randomisation	Intervention/Treatment period (event driven)										EoT	EoS
				First year						Remaining years					
Visit		V1	V2	V3	P4[b]	V5	V6	V7	V8	P9[b], P11[b], P13[b], P15[b], P17[b]	V10, V14, V18[c]	V12	V16	V-EoT	V-EoS
Timing of visit (months unless otherwise specified)		Up to - 5 wks[d]	0	1	2	3	6	9	12	15, 21, 27, 33, 39	18, 30, 42	24	36	EoT	EoT+ 3 mos
Visit window (days)				±3	±3	±3	±7	±7	±7	±10	±10	±10	±10		+10
Patient Global Impression of Severity - KCCQ[k]	8.1.2.1		X				X		X						
Patient Global Impression of Change – KCCQ[k]	8.1.2.1						X		X						
EQ-5D-5L[k]	8.11.1		X				X		X						
Subject Participation Feedback Questionnaire (SPFQ) *(optional)*[k]	8.12.1		X						X					X	
Study Check-In (SCI) (*optional*)[k]	8.12.2		X				X		X		X	X	X		
CardioSignal app (*optional*) evaluation[l, m]	8.12.3		X	X	X	X	X	X	X	X	X	X	X	X	X
Hospitalisation	8.1.4.1		X	X	X	X	X	X	X	X	X	X	X	X	X
Height	8.2.1		X												
Body weight	8.2.1		X						X			X	X	X	X
Waist circumference	8.2.1		X						X						
Physical examination	8.2.1		X						X			X	X	X	
Vital signs	8.2.2	X	X	X		X	X	X	X		X	X	X	X	X
NYHA	8.1.3.1	X	X			X	X		X			X		X	
Adverse events and other safety reporting	8.3		X	X	X	X	X	X	X	X	X	X	X	X	X
LABORATORY ASSESSMENTS (non-fasting)															
hs-CRP	8.1.1	X[a]	X	X		X	X		X		X	X	X	X	X
IL-6	8.1.1		X												
NT-proBNP	8.1.1	X[a]	X			X			X					X	

Procedure/period	Protocol section	Screening period[a]	Randomisation	Intervention/Treatment period (event driven)										EoT	EoS
				First year						Remaining years					
Visit		V1	V2	V3	P4[b]	V5	V6	V7	V8	P9[b], P11[b], P13[b], P15[b], P17[b]	V10, V14, V18[c]	V12	V16	V-EoT	V-EoS
Timing of visit (months unless otherwise specified)		Up to - 5 wks[d]	0	1	2	3	6	9	12	15, 21, 27, 33, 39	18, 30, 42	24	36	EoT	EoT+ 3 mos
Visit window (days)				±3	±3	±3	±7	±7	±7	±10	±10	±10	±10		+10
eGFR (CKD-EPI[10])	8.1.1	X	X	X		X	X	X	X		X	X	X	X	X
Lipids	8.2.4		X	X		X			X			X	X	X	X
HbA_{1c}	8.2.4		X						X			X			
Biochemistry, haematology[n]	8.2.4	X[o]	X	X		X	X	X	X		X	X	X	X	X
PK sampling[p]	8.4		X	X		X	X		X		X	X	X	X	X
Blood samples for future analysis (genetics)[l] *(optional)*	8.7		X									X		X[q]	
Blood samples for future analysis (biomarkers)[l] *(optional)*	8.8		X			X			X						
TRIAL MATERIAL															
Training in administration of study intervention and dosing instructions[r] and supervised self-administration of study intervention during the study visit[s]	6.2.1		X	X		X									
Dispensing of study intervention via RTSM/IWRS	6.2.1		X[t]	X		X	X	X	X	X[u]	X	X	X		
OTHER ACTIVITIES															
Download study app and receive training in its use	8		X												
Ensure updated contact persons list	8	X	X	X	X	X	X	X	X	X	X	X	X	X	

[a] Screening can be performed at one or more visits to the clinic, at the discretion of the investigator. The date of visit 1 will be the date of the initial visit to the clinic, i.e., the date where informed consent is obtained. Note that the screening ECG must be obtained the same day as sampling for NT-proBNP for assessment of inclusion criterion #4;

[b] Planned phone visits can be converted to site visits at the discretion of the investigator. Note that if visit is performed as phone visit, the study intervention is to be picked-up at the study site or delivered to the participant; see Section 6.2 for details;
[c] If the event rate is lower than anticipated, then visits and related assessments will be repeated every 3 months beyond V18 until the necessary number of primary outcome events have been accrued;
[d] If the participant has history or evidence of untreated latent TB at screening and treatment for latent TB is initiated during screening, the screening period can be extended from 5 weeks to a maximum of 8 weeks. This is to allow for at least 28 days of treatment before randomisation without the need for re-screening the participant;
[e] Demography consists of date of birth, sex, ethnicity and race (according to local regulation). Local requirements may apply. Czech Republic, France, Germany, Hungary, Lithuania, Netherlands, Portugal, Spain, Taiwan: see country/region-specific requirements (Appendix 11, Section 10.11). Race and ethnicity must be self-reported by the participant;
[f] To be evaluated as part of eligibility criteria, but not to be recorded in eCRF;
[g] Infection serology will include screening for hepatitis B and C. Local requirements may apply. Argentina: see country/region-specific requirements (Appendix 11, Section 10.11). HBsAg, Anti-HBc, HBV DNA (only in participants with positive anti-HBc) to be assessed at screening. Anti-HBc positive, but HBV DNA negative participants should be monitored with HBV DNA at the indicated timepoints during the study;
[h] Only applicable for women of childbearing potential (WOCBP). Local urine testing will be standard unless serum testing is required by local regulation or IRB/IEC. If the study visit is a phone contact, the participant can take the urine test at home and inform the investigator of the result. Home pregnancy kits will be provided. Local requirements for monthly testing in WOCBP may apply. Austria, Argentina, Czech Republic, Germany, Italy, Portugal, Romania, South Korea, UK: see country-specific requirements (Appendix 11, Section 10.11);
[i] ECG to be performed to assess presence of ongoing atrial fibrillation or flutter and evaluation of inclusion criterion #4;
[j] Echocardiography is optional if participant is in a stable condition and recent (within 12 months before screening – visit 1) documented echocardiography is available in medical records;
[k] The questionnaires should be completed in close relation to the visit, i.e., prior to or at the visit. Participants should be given the opportunity to complete the questionnaires by themselves without interruption;
[l] Separate informed consent required;
[m] Note, this option is only available for selected countries based on CardioSignal app registration status (Section 8.12.3). Participants should download the CardioSignal app at V2 and receive training in its use before collecting any data. The app should be used by the participants between visits, in accordance with agreements between the participant and investigator. Relevant findings from the app should be discussed with the participant at a visit, and appropriate actions should be taken at the discretion of the investigator. Local requirements may apply. Portugal: see country/region-specific requirements (Appendix 11, Section 10.11);
[n] Some haematology and biochemistry assessments are performed less frequently. Haematology: haematocrit, MCH, MCHC, MCV and reticulocyte count. Biochemistry: transferrin, transferrin saturation, ferritin and haptoglobin at V2, V5 and V8 only;
[o] Only parameters needed for evaluation of in- and exclusion criteria will be analysed and assessed;
[p] Samples will also be used for anti-drug antibody analysis in case of suspected hypersensitivity reaction, if relevant for overall PK / PD assessment or if requested by Health Authorities;
[q] EoT sample is only to be obtained in participants without a 24 month (V12) sample;
[r] Training in use of device and administration of study intervention until competence is demonstrated; optional training at later visits upon request from user or at the discretion of the investigator;
[s] At visits 2, 3 and 5, study intervention will be administered by the participant, under the supervision of the investigator, during the study visit after all assessments have been completed. At all other timepoints, the study intervention will be self-administered by the participant;
[t] No hand-out of study intervention to the participant at visit 2;
[u] The dispensing options will be based on options and requirements at country/region level and if permitted by local regulations. A non-participating person may collect the allocated study

intervention on behalf of the participant. If study intervention is collected by a non-participant, this must be agreed with the participant on beforehand and thoroughly documented at the site e.g., by means of a letter of authorisation issued by the participant, and, on each occasion, the investigator must follow up by contacting the participant. Alternatively the phone contact should be converted to a site visit.

Abbreviations: Anti-HBc = hepatitis B core antibody; CKD-EPI = chronic kidney disease – epidemiology collaboration; eCRF = electronic case report form; eGFR = estimated glomerular filtration rate; EoT = end of treatment visit; EoS = end of study at the end of the follow-up period; EQ-5D-5L = EuroQoL five dimensions five level questionnaire; HBsAg = Hepatitis B surface antigen; HBV = hepatitis B virus; hs-CRP = high-sensitivity C-reactive protein; IL-6 = interleukin 6; IRB/IEC = institutional review board/independent ethics committee; KCCQ = Kansas City Cardiomyopathy Questionnaire; MCH = mean corpuscular haemoglobin; MCHC = mean corpuscular haemoglobin concentration; MCV = mean corpuscular volume, mos = months; NT-proBNP = N-terminal-pro-brain natriuretic peptide; NYHA =New York Heart Association (classification); PD = pharmacodynamics; PK = pharmacokinetics; RTSM/IWRS = randomisation and trial supplies management/interactive web response system; SCI = Study Check-In; SPFQ = Subject Participation Feedback Questionnaire; TB = tuberculosis; wks = weeks.

Local requirements may apply; see country/region-specific requirements (Appendix 11, Section 10.11).

2 Introduction

2.1 Study rationale

Chronic heart failure (HF) is recognised as a complex clinical syndrome associated with a wide range of abnormalities in cardiac structure or function. HF can be broadly described as the failure of the heart to supply blood to either systemic or pulmonary circulation at an appropriate rate of flow, or to receive venous return at an appropriate filling pressure, resulting in adverse effects on the heart, the circulation, and the patient.

HF affects approximately 2% of the adult population in developed countries and approximately 64.3 million patients worldwide.[2-4] The risk of developing HF increases sharply with increasing age, and the general aging of the global population will result in more patients living with HF.[11]

HF causes substantial mortality and morbidity and has major effects on physical function and quality of life.[5, 6] Despite optimal management, a considerable residual risk of severe events remains, and patients with chronic heart failure (CHF) have troublesome symptoms, including dyspnoea and fatigue.

The diagnosis of HF is currently classified based on left ventricular ejection fraction (LVEF). The primary phenotypes of CHF are HF with reduced ejection fraction (HFrEF) (LVEF ≤40%), HF with mildly reduced ejection fraction (HFmrEF) (LVEF of 41-49%) and HF with preserved ejection fraction (HFpEF) (LVEF ≥50%).[2, 3] HFmrEF and HFpEF represents approximately half of HF cases[7] and the proportion being classified as HFpEF has increased in the last decade.[8] To date, limited pharmacological interventions to address HFmrEF and HFpEF have been approved. Current treatment options include ARNi (sacubitril/valsartan) (currently only approved in US for HFmrEF and HFpEF) and SGLT2i (empagliflozin). A CVOT within HFmrEF and HFpEF is currently ongoing with the mineralocorticoid receptor antagonist finerenone. Treatment guidelines also recommend treatment of risk factors, e.g., drug therapy for blood pressure control and as needed use of diuretics for HF exacerbation episodes to ensure optimisation of the patient's volume status.[2, 3, 12] Current HF therapies in patients with HFmrEF and HFpEF is thus limited, making it one of the greatest unmet needs in cardiology today.[8]

Development and severity of HF, in particular HFpEF, has been linked to systemic inflammation.[13] Elevated concentrations of IL-6 have been associated with disease severity and mortality in CHF. In the BIOSTAT-CHF study[14], HFmrEF and HFpEF was associated with high IL-6 levels and in patients with CHF the IL-6 level was a predictor of all-cause mortality and HF hospitalisation. Furthermore, IL-6 has been identified as a predictor of new-onset HFmrEF and HFpEF in two community-based studies.[15, 16] No randomised controlled trials have been conducted investigating IL-6 inhibition in the HFpEF population. However, there is key evidence from a prespecified exploratory analysis of the CANTOS study which investigated the interleukin-1β inhibitor (IL-1βi) canakinumab, IL-1β is upstream of IL-6, where a dose-dependent reduction in time to first HF hospitalisation was observed (24% reduction with the 300 mg dose).[17] A similar effect was observed regardless of medical history of HF, but no data on the HF subtype is available. This effect was likely driven by inhibition of IL-6 similar to the primary outcome of MACE. Overall, pathophysiological, epidemiological and clinical data support inflammation including IL-6 as a key driver of progression and worse outcomes in HFpEF.

Ziltivekimab is a human monoclonal antibody directed against the IL-6 ligand. Ziltivekimab once-monthly has been shown to reduce inflammation as measured by high-sensitivity C-reactive protein (hs-CRP)[9], in patients with chronic kidney disease (CKD) and systemic inflammation; see current version of the ziltivekimab investigator's brochure[9] and any updates thereof.

Several pathophysiological pathways have been proposed linking systemic inflammation to the development and worsening of HFmrEF and HFpEF. Ziltivekimab has the potential to interfere with the principal pathophysiological derangements in HFmrEF and HFpEF, and thereby improve survival and outcomes in patients with HFmrEF or HFpEF (i.e., with LVEF >40%). Hence, the key differentiator to current treatment options is thus targeting the inflammatory pathology of HF in patients with HFmrEF or HFpEF.

In order to evaluate the effects of ziltivekimab on morbidity and mortality of patients with HFmrEF or HFpEF and systemic inflammation, the current study was designed as a CVOT evaluating ziltivekimab versus placebo (randomised 1:1), both administered in addition to standard of care (SoC).

2.2 Background

HFmrEF and HFpEF is a multiorgan, systemic syndrome made up of multiple pathophysiological abnormalities above and beyond left ventricular (LV) diastolic dysfunction.[18] Several physiological mechanisms are involved, including myocardial hypertrophy and fibrosis[19], impaired diastolic compliance and relaxation[20], subclinical systolic dysfunction[21], and renal dysfunction leading to elevated intracardiac filling pressures, fluid retention, and exercise intolerance.

The principal biological processes that characterise HFmrEF and HFpEF are systemic inflammation (linked to both cardiac and renal fibrosis), epicardial adipose tissue accumulation, coronary microcirculatory rarefaction, myocardial fibrosis and vascular stiffness.[19, 22-25] For further details on the immuno-metabolic mechanisms of HFpEF, please refer to the review by Schiattarella et al.[26]

It is suggested that coronary microvascular inflammation is induced as part of a systemic inflammatory response to coexisting conditions[8], especially metabolic conditions like obesity, hyperglycaemia, dyslipidaemia and hypertension.[27] For further details on inflammation biology in the setting of HF, please refer to the published overview by Paulus.[8]

Several pathophysiological pathways have been proposed leading from systemic inflammation to diastolic left ventricular stiffness and HFpEF.[8] The resulting impairment of left ventricular and aortic distensibility (especially when accompanied by impaired glomerular function and sodium retention) causes increases in cardiac filling pressures and exertional dyspnoea despite the relative preservation of left ventricular ejection fraction (LVEF).[28] The systemic inflammation in HFmrEF and HFpEF can also cause changes in mitochondrial function and in the mass and composition of skeletal muscle[29], which can contribute to exercise intolerance in this disorder.

Being one of these comorbidities, CKD is a pro-inflammatory state, and shares much of pathophysiology seen in HFpEF.[30] In CKD, the plasma level of IL-6 increases with increasing severity, and a high IL-6 level independently predicts overall mortality and cardiovascular mortality.[31] Another marker of systemic inflammation and kidney damage is albuminuria, which is a strong predictor of new onset HFpEF and adverse outcomes in HFpEF.[32]

Nonclinical studies support the role of IL-6 in HFpEF. IL-6 infusion in rats has been associated with myocardial fibrosis, concentric hypertrophy, and diastolic dysfunction. Deletion of IL-6 in mice, attenuates pressure overload-induced LV hypertrophy and dysfunction.[33]

In humans, IL-6 is associated with biological processes involved in cardiomyocyte relaxation in HFpEF patients and correlated with LV diastolic function. Biomarkers related to subclinical inflammation and oxidative stress have been found to be elevated in patients with HFpEF as compared to healthy subjects.[34]

No randomised controlled trials have been conducted investigating IL-6 inhibition in the HFpEF population. The IL-1 receptor antagonist anakinra has been investigated in the D-HART pilot study and D-HART2 study in patients with HFpEF and the IL-1β inhibitor canakinumab has been investigated for HF endpoints in a prespecified exploratory analysis of the CANTOS study in a patient population with prior myocardial infarction and elevated hs-CRP levels. In CANTOS[17], canakinumab was associated with a significant dose-dependent trend in reduced rates of HF hospitalisations and the composite of HF hospitalisation or HF-related mortality.

In view of the pathophysiological, epidemiological and clinical data summarised above, it is hypothesised that direct IL-6 inhibition is an effective target for the reduction of systemic inflammation and may ultimately lead to reduced risk of CV death and HF events, especially in a population with established HFmrEF or HFpEF and systemic inflammation. Accordingly, the development of a specific anti-IL-6 therapy for patients with HFmrEF or HFpEF and systemic inflammation may offer clinically relevant benefit in this population who remain at high residual risk, despite optimal guideline directed medical therapy.

A high-risk population of patients with HFmrEF or HFpEF, elevated NT-proBNP and systemic inflammation is an appropriate target population for a risk reduction intervention and will ensure that the primary objective of the study can be investigated within a reasonable timeframe and sample size.

Vulnerable patients, including pregnant or breast-feeding women, and patients unlikely to complete the study due to pre-existing severe clinical conditions are excluded from the study.

2.3 Benefit-risk assessment

The main benefits and risks related to participation in the study, as identified at initiation of the study, are described in the below sections. More detailed information about the known and expected benefits and risks and reasonably expected adverse events of ziltivekimab may be found in the current edition of the investigator's brochure[9] or updates thereof.

2.3.1 Risk assessment

Ziltivekimab is being developed as an anti-inflammatory therapeutic targeting a specific and downstream component of the complex inflammatory cascade to minimise the risk of side effects such as increased occurrence or reoccurrence of infections. Currently, there are no identified risks with ziltivekimab.

The sections below describe potential risks associated with ziltivekimab treatment. The potential risks are based on findings in nonclinical studies and clinical studies with ziltivekimab (s.c. as well

as i.v.) as well as other anti-IL-6/IL-6R products including SYLVANT® (siltuximab)[35], ACTEMRA® (tocilizumab)[36], and KEVZARA® (sarilumab).[37] For each of these risks, mitigating actions have been implemented to minimise the risks for participants enrolled in this study (Table 2-1).

Nonclinical toxicology studies have established the no observed adverse effect level (NOAEL) by the maximal dose administered. Both in terms of local and systemic effects, ziltivekimab was well tolerated, with no apparent adverse findings. Of note, the ziltivekimab 15 mg dose planned for this study will provide exposure ratios of 270-fold to C_{max} and 304-fold to AUC at steady-state compared to the s.c. NOAEL established in nonclinical toxicology programme.

Table 2-1 Risk assessment

Potential risk of clinical significance	Summary of data/ rationale for risk	Mitigation and monitoring strategy
Study intervention: ziltivekimab		
Potential risk: Infections	Section 2.3.1.1	As a precaution, potential participants with active infections, history of recurrent serious infections, or untreated latent tuberculosis, active hepatitis B or C, HIV (not on stable antiretroviral regimen), or use of preventive systemic antibiotics will not be enrolled in this study. Antibiotics used to treat latent tuberculosis are exempted. Diagnosis of HIV (not on stable antiretroviral regimen), untreated latent tuberculosis, active hepatitis B or C as well as serious infections (infections leading to hospitalisation or use of i.v. antibiotics) or opportunistic infections[38] during the study will lead to temporary or permanent discontinuation[a] of study intervention. Furthermore, live or attenuated-live vaccine products should not be administered together with study intervention. To minimise the risk, standard safety surveillance activities and medical monitoring will be performed by Novo Nordisk.
Potential risk: Neutropenia	Section 2.3.1.2	As a precaution, potential participants with an absolute neutrophil count $<2\times10^9$/L will not be enrolled in this study. Furthermore, study intervention should be temporarily discontinued[a] if absolute neutrophil count $<1\times10^9$/L is recorded during the study. To minimise the risk, standard safety surveillance activities and medical monitoring will be performed by Novo Nordisk.
Potential risk: Thrombocytopenia	Section 2.3.1.3	As a precaution, potential participants with a platelet count $<120\times10^9$/L will not be enrolled in this study. Furthermore, study intervention should be temporarily discontinued[a] if platelet count $<100\times10^9$/L is recorded during the study. To minimise the risk, standard safety surveillance activities and medical monitoring will be performed by Novo Nordisk.
Potential risk: Elevated liver enzymes	Section 2.3.1.4	As a precaution, potential participants with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.5 × upper limit of normal will not be enrolled in this study. Furthermore, study intervention should be temporarily discontinued[a] if abnormal liver blood parameters indicating drug induced liver injury (DILI) is recorded during the study. To minimise the risk, standard safety surveillance activities and medical monitoring will be performed by Novo Nordisk.
Potential risk: Lipid abnormalities	Section 2.3.1.5	Participants will be followed closely and carefully by qualified medical staff.

Potential risk of clinical significance	Summary of data/ rationale for risk	Mitigation and monitoring strategy
		To minimise the risk, standard safety surveillance activities and medical monitoring will be performed by Novo Nordisk. Furthermore, optimisation of standard of care will be recommended throughout the study.
Potential risk: Gastrointestinal perforation	Section 2.3.1.6	As a precaution, potential participants with a history of gastrointestinal perforation, active diverticulitis (within 5 years) or active inflammatory bowel disease (within 12 months) prior to randomisation will not be enrolled in this study. Furthermore, study intervention should be permanently discontinued[a] if an event of gastrointestinal perforation or active diverticulitis is recorded during the study. To minimise the risk, standard safety surveillance activities will be performed by Novo Nordisk.
Potential risk: Injection site reactions	Section 2.3.1.7	Participants are instructed by the investigators on the most appropriate injection techniques and the initial injections are performed by the participant under supervision during the study visit. Standard safety surveillance activities will be performed by Novo Nordisk.
Potential risk: Immunogenicity	Section 2.3.1.8	*Hypersensitivity* As a precaution, potential participants with known or suspected hypersensitivity to ziltivekimab or related products will not be enrolled in this study. Furthermore, study intervention should be permanently discontinued[a] if hypersensitivity reactions are suspected during the study. Participants will be instructed to contact the site staff as soon as possible for further guidance, if suspicion of a hypersensitivity reaction to the study intervention occurs. To minimise the risk, standard safety surveillance activities will be performed by Novo Nordisk.
Study procedures		
Risk of COVID-19 infection in relation to participation in study	Section 2.3.1.9	To minimise the risk, Appendix 10 (Section 10.10) includes mitigations that can be implemented to ensure the safety of the participants and data integrity in case a COVID-19 outbreak leads to lockdown of a site or pharmacy or a restriction of movement of participants, which affects the ability to perform study-related procedures.
Other		
Pregnancy and fertility	Section 2.3.1.10	Ziltivekimab should not be used during pregnancy. Women of childbearing potential are required to use highly effective contraceptive methods when participating in this study (Appendix 4, Section 10.4). If a female participant wishes to become pregnant, or pregnancy occurs during the study, treatment with study intervention should be discontinued[a] immediately. Highly effective contraception to be utilised for at least 5 half-lives (285 days - 10 months) after last dose of study intervention. Please refer to Section 7.1.1 for further guidance. The effect of ziltivekimab on fertility in humans is unknown.
Drug-drug interactions	Section 2.3.1.11	Caution should be taken when ziltivekimab is co-administered with CYP450 and CYP3A4 substrate drugs (see Section 6.8.3 for details).

Note: [a] Please refer to Section 7.1.1 for details.
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CYP3A4 = cytochrome 3A4; DILI = drug-induced liver injury; HIV = human immunodeficiency virus.

2.3.1.1 Infections

Anti-inflammatory therapies in general run the risk of inducing immune suppression and promoting the emergence of infections, sometimes serious in nature. There is no firm evidence of the effect of ziltivekimab on COVID-19 susceptibility or severity.

Although anti-IL-6 therapies lower neutrophil counts and may induce neutropenia, rates of infectious complications appear to be similar to other immune-modulatory biologic agents when accounting for patient-specific factors.[39] In the completed ziltivekimab phase 2 dose-finding studies (denoted RESCUE), no imbalances were observed in proportion of participants with serious infections. In RESCUE-US, 7 events (10.8%) were reported with ziltivekimab 7.5 mg: 3 events (4.5%); with ziltivekimab 15 mg, 2 events (3.1%) with ziltivekimab 30 mg versus 3 events (4.6%) with placebo.[9]

As a precaution, potential participants with active infections (exclusion criterion #23), history of recurrent serious infections (exclusion criterion #24), HIV (not on stable antiretroviral regimen)(exclusion criterion #25), active hepatitis B or C (exclusion criterion #12), untreated latent tuberculosis (exclusion criterion #26), or use of preventive systemic antibiotics (exclusion criterion #34) at screening are not eligible for enrolment in the study. Antibiotics used to treat latent tuberculosis are exempted.

Participants will be monitored closely throughout the study for infections, and any infections, including localised infections, are to be treated promptly using local standard of care (see Section 8.2.6 for details). In case of serious infection during the study period, study intervention is to be temporary discontinued until the infection is controlled (discontinuation criterion #8). Furthermore, diagnosis of HIV (not on stable antiretroviral regimen), untreated latent tuberculosis, active hepatitis B or C will lead to temporary or permanent discontinuation of study intervention (discontinuation criteria #1, 6, 7).

Participants will be informed about general and local signs of infection to draw attention to, and that vigilance for timely detection of infections is needed, as signs and symptoms of acute inflammation may be lessened because of suppression of the acute-phase immune reaction. Participants will be provided with an ID card informing about the study and that the participant may be receiving an anti-inflammatory agent. Information and cautions to be taken when handling infections during ziltivekimab administration has been issued by a group of experts in infectious diseases and are provided in a separate document.

Live or attenuated-live vaccine products should not be administered together with study intervention (see exclusion criterion #33 and discontinuation criterion #13) because IL-6 inhibition may impact the magnitude of an immune response to new antigens. For guidance refer to Appendix 9 (Section 10.9). If such vaccines are needed, study intervention should be paused for a minimum of 3 months before the live / attenuated-live vaccine is administered, and study intervention can be administered one month after the vaccination.

Not-live and not attenuated-live vaccines are allowed during study conduct without pausing study intervention. Participants should be informed that receiving a not-live or not attenuated-live vaccine concurrently with study intervention may give a suboptimal or slower immune response.

Furthermore, use of systemic immunosuppressive drugs in combination with study intervention is not allowed in the study (exclusion criterion #35 and discontinuation criterion #12).

2.3.1.2 Neutropenia

Lowering of neutrophil counts and development of neutropenia have been reported with marketed anti-IL-6 therapies and ziltivekimab, although ziltivekimab seems to result in a smaller decrease compared to the other compounds. A dose-dependent decrease in neutrophil count has been observed with ziltivekimab in clinical studies. In the RESCUE studies, no participants had sustained (at least 2 consecutive visits) neutropenia grade 3 or worse (neutrophil count<1×10^9/L) and few had grades 1 or 2 sustained neutropenia.[9] Furthermore, observed decreases in neutrophil counts were not associated with adverse events of infections and infestations.

Potential participants with an absolute neutrophil count <2×10^9/L at screening (visit 1) are not eligible for the study (exclusion criterion #9). Furthermore, study intervention should be temporarily discontinued if absolute neutrophil count <1×10^9/L is recorded during the study (discontinuation criterion #9). Administration of study intervention may be initiated if neutrophil counts return to normal (see Section 7.1.1 for details).

2.3.1.3 Thrombocytopenia

Lowering of platelet counts and development of thrombocytopenia have been reported with marketed anti-IL-6/IL-6R therapies and with ziltivekimab.[9] Small, dose-dependent decreases in platelet counts were observed with ziltivekimab in the RESCUE studies.[9] No participants had sustained (at least 2 consecutive visits) thrombocytopenia grade 2 or worse (platelet count<75×10^9/L), and few had grade 1 sustained thrombocytopenia. The observed decreases in platelet counts with ziltivekimab were not associated with adverse events of bleeding; no events of moderate thrombocytopenia with evidence of concurrent major bleeding were reported. No events of sustained thrombocytopenia or major bleeding were reported in RESCUE-JP.[9]

Potential participants with platelet count <120×10^9/L at screening (visit 1) are not eligible for the study (exclusion criterion #10). Furthermore, study intervention should be temporarily discontinued if a platelet count <100×10^9/L is recorded during the study (discontinuation criterion #10). Administration of study intervention may be initiated if platelet counts return to normal (see Section 7.1.1 for details).

2.3.1.4 Elevated liver enzymes

Elevation of levels of liver enzymes have been reported with marketed anti-IL-6 therapies and with ziltivekimab.[9] In the RESCUE studies, marginal elevations in liver enzyme (AST/ALT) levels were observed with ziltivekimab. Few participants had AST and/or ALT above the upper normal range, however, none had levels more than 3 times the upper normal range. No participants had elevation in liver enzymes leading to premature discontinuation of study intervention.

Ziltivekimab has not been studied in patients with advanced hepatic failure (end stage liver disease). Potential participants with AST or ALT > 2.5x the upper limit of normal during screening will be excluded from the study (exclusion criterion #11). Furthermore, study intervention should be temporarily discontinued if abnormal liver blood parameters indicating drug induced liver injury (DILI[40]) are recorded during the study (discontinuation criterion #11).

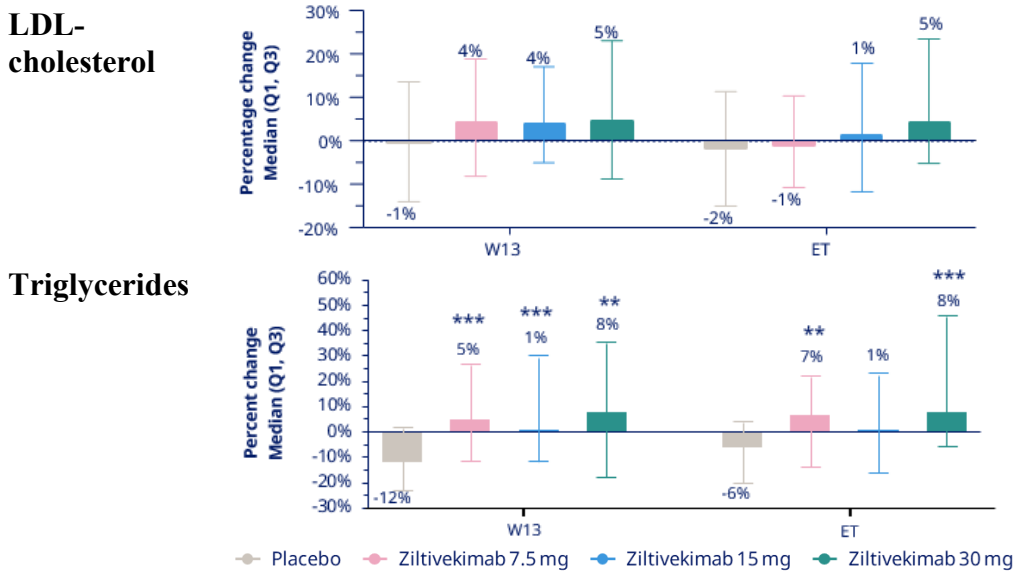
2.3.1.5 Lipid abnormalities

Elevation of total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides have been observed with marketed anti-IL-6/IL-6R therapies.

Levels of LDL-cholesterol, triglycerides and apolipoprotein B were slightly increased with ziltivekimab at all dose levels in the RESCUE-US study[9] (Figure 2-1). Similar findings were evident in RESCUE-JP with increases in LDL-cholesterol and triglycerides.[9]

In RESCUE-US, the increase in levels of LDL-cholesterol, triglycerides and apolipoprotein B appeared to be more pronounced with ziltivekimab 30 mg, than with lower ziltivekimab dose levels (Figure 2-1). In RESCUE-JP, increased in LDL-cholesterol with ziltivekimab did not appear to be dose related, whereas increases in triglycerides with ziltivekimab appeared to be dose-dependent.

Figure 2-1 Change (%) in levels of LDL-cholesterol and triglyceride after12 weeks of treatment (week 13 visit) and end of treatment – RESCUE-US



Note: Study intervention was administered at weeks 1, 5, 9, 13, 17, and 21. Percent change is shown as median (Q1/Q3).
Abbreviations: ET = end of treatment; W13 = week 13 visit after 12 weeks of treatment.

In RESCUE-US, improvements in HDL-cholesterol were observed with ziltivekimab across all dose levels.[9] In RESCUE-JP, a neutral effect on HDL-cholesterol was observed with ziltivekimab.[9]

Both in RESCUE-US[41] and in RESCUE-JP, ziltivekimab did not have a significant effect on total cholesterol to HDL-cholesterol ratio.[9]

Lipid levels will be assessed throughout the study, and monitoring of changes in lipid parameters (e.g., hypercholesterolemia, hypertriglyceridemia) will be performed as part of the standard safety surveillance activities and medical monitoring by Novo Nordisk. Standard of care therapy, including lipid-lowering treatment, are to be provided and optimised throughout this study. Recommendations for standard of care will be provided in guidance documents from the steering committee (StC) and global expert panel (GEP) during study conduct.

2.3.1.6 Gastrointestinal perforation

Events of gastrointestinal perforation have been reported in clinical studies of marketed anti-IL-6/IL-6R therapies, primarily as complications of diverticulitis in patients with rheumatoid arthritis.[42] One event of perforated appendicitis has been reported with ziltivekimab in a completed phase 1/2 study in participants on haemodialysis.[9] No events of gastrointestinal perforation have been reported with ziltivekimab in the completed RESCUE studies[9], however, a potential risk cannot be excluded.

Data from marketed anti-IL-6/IL-6R therapies suggest, that robust exclusion criteria may mitigate these risks. Hence, in the current study, potential participants with history of gastrointestinal perforation, active diverticulitis (within 5 years) or active inflammatory bowel disease (within 12 months) prior to randomisation will not be eligible for inclusion (exclusion criteria 28# to #30). Furthermore, study intervention should be permanently discontinued if an event of gastrointestinal perforation or active diverticulitis is recorded during the study (discontinuation criterion #3).

2.3.1.7 Injection site reactions

Study participants may experience injection-site reactions like erythema and pruritus, as study intervention (ziltivekimab or placebo) is administered as a s.c. injection.

No adverse events indicating severe allergic reactions at injection site, i.e., erythema, pruritus, swelling or rash at injection site, or severe (CTCAE Grade ≥3) injection-related reactions were reported in the RESCUE studies.[9]

Few and mild injection site reactions were reported in the completed studies with ziltivekimab evaluating up to 3 dose levels of s.c. ziltivekimab (7.5 mg, 15 mg and 30 mg administered using vial and syringe) in participants with CKD and systemic inflammation.[9] In RESCUE-US, one participant (zilti 15 mg) reported an adverse event of injection site pain (mild) in left arm. In RESCUE-JP, one participant (zilti 15 mg) reported mild events of injection site swelling and injection site pruritis in relation to each of the 3 administrations of study intervention. Furthermore, one participant (zilti 15 mg) reported mild injection site pruritus, and one participant (zilti 30 mg) reported an event of mild infusion site reaction (evaluated by the investigator as unrelated to study intervention).

Study participants are instructed by the investigators on the most appropriate injection techniques and the initial injections are performed by the participant under supervision during the study visit, as described in the flowchart (Section 1.2).

2.3.1.8 Immunogenicity

The immunogenicity risk of ziltivekimab is assessed to be low, see below.

Hypersensitivity

As expected for a protein-based drug, participants treated with ziltivekimab may develop localised (to the injection site) or generalised immune and hypersensitivity reactions including urticaria, rash or pruritus. Severe hypersensitivity reactions such as anaphylactic reactions could potentially also pose a risk to participants treated with ziltivekimab. Data from both the completed clinical studies with ziltivekimab and other anti-IL-6 or anti-IL-6 receptor therapies, indicate that the potential risk

of hypersensitivity reactions is low.[9] No signs or evidence of hypersensitivity reactions have been reported with ziltivekimab in the completed RESCUE studies.[9]

Potential participants with known or suspected hypersensitivity to study intervention or related products will be excluded from the study (exclusion criterion #1). Furthermore, study intervention should be permanently discontinued if severe systemic hypersensitivity reactions are suspected during the study (discontinuation criterion #2). In case of a systemic hypersensitivity reaction, digital pictures and blood sampling for assessment of antibodies against ziltivekimab, as well as other assessments is recommended (Section 8.6.1). In addition, participants will be instructed to contact the site staff as soon as possible for further guidance, if suspicion of a hypersensitivity reaction to the study intervention occurs.

Formation of anti-ziltivekimab-antibodies leading to changes in clinical effect

Ziltivekimab has no endogenous counterpart and binds to a soluble target (IL-6), i.e., there is no risk of antibody-dependent cellular cytotoxicity.

In RESCUE-US, 8.7% of participants developed anti-ziltivekimab antibodies across dose groups.[9] In RESCUE-JP, all participants tested negative on anti-ziltivekimab antibodies.[9] The frequency of anti-ziltivekimab antibody (ADA) development is comparable to what is found for marketed anti-IL-6/IL-6R therapies and other anti-IL-6 mAbs in clinical development (2-10%).[43]

In vitro neutralising antibodies (nAb) was not assessed in RESCUE-US.[9] One case (0.5%) of high titre anti-ziltivekimab antibodies was observed in RESCUE-US. The high titre ADAs reduced the concentration of measurable ziltivekimab which likely caused hs-CRP to increase to baseline level. Based on this one case, it is not possible to determine if the clinical effects were also affected.

2.3.1.9 Risk of COVID-19 infection in relation to participation in study

Study participants may be exposed to the risk of COVID-19 transmission and infection in relation to site visits if an outbreak is ongoing in the given country/region.

The risk of COVID-19 transmission in relation to site visits is overall considered to be low; however, this may vary between geographical areas. To minimise the risk as much as possible, the following measures have been taken:

- Cautious recruitment planning to ensure controlled enrolment in countries where the COVID-19 pandemic is evaluated to be sufficiently under control, and at sites where health care resources are evaluated to be adequate.
- Physical contact between participants and site staff will be limited to the extent possible, and protective measures will be implemented according to local practice.

Appendix 10 (Section 10.10) includes mitigations that can be implemented to ensure the safety of study participants and data integrity in case a COVID-19 outbreak leads to lockdown of a site or pharmacy or a restriction of movement of participants which affects the ability to perform study-related procedures.

There is no firm evidence of the effect of ziltivekimab on COVID-19 susceptibility or severity. Please refer to Section 2.3.1.1 regarding infections in general.

2.3.1.10 Pregnancy and fertility

Studies evaluating the potential for reproductive and developmental toxicity of ziltivekimab have not been performed. Therefore, ziltivekimab should not be used during pregnancy.

Women who are pregnant at screening or are planning or attempting to become pregnant are not eligible for enrolment in the study (exclusion criterion #3). Hence, for women of childbearing potential a negative pregnancy test is required at screening, at randomisation and at all visits during the study. Furthermore, women of childbearing potential not using an adequate and highly effective contraceptive method (exclusion criterion #3) are excluded from the study.

If a female participant wishes to become pregnant, or pregnancy occurs during the study, treatment with study intervention should be discontinued immediately (discontinuation criteria #4 and #5). Highly effective contraception to be utilised for at least 5 half-lives (285 days - 10 months) after last dose of study intervention.

2.3.1.11 Drug-drug interactions

Formal drug-drug interaction studies with ziltivekimab have not been conducted. Ziltivekimab is not expected to affect the metabolic pathways of most drugs.

IL-6 modulators may restore CYP450 activities to normal levels leading to increased metabolism of drugs that are CYP450 substrates compared to metabolism prior to treatment with IL-6 modulators. However, there is a low risk of clinically relevant drug-drug interactions related to CYP450 enzymes because of a reduction in IL-6 concentration levels following treatment with ziltivekimab. Caution should be taken when ziltivekimab is co-administered with CYP3A4 substrate drugs where a decrease in effectiveness would be undesirable (see Section 6.8.3 for details).

2.3.2 Benefit assessment

It is expected that all participants, including those randomised to placebo, will benefit from participation in the study through frequent, close contact with investigators and other site staff who will ensure that disease development and progression will be closely monitored and treated following careful medical examinations of each participant.

During the current study, all participants will be treated with a regimen anticipated to be better than or equal to the treatment they receive at the time of entry into the study. To ensure all participants, including those receiving placebo have an adequate treatment of HFmrEF or HFpEF and related risk factors and underlying diseases, investigators are encouraged to optimise participant treatment in accordance with standard of care and with local clinical practice throughout the study. Recommendations for standard of care will be provided in guidance documents from the steering committee (StC) and global expert panel (GEP) during study conduct.

In completed clinical studies ziltivekimab has shown a reduction in systemic inflammation, as assessed by hs-CRP, in participants with CKD. Ziltivekimab may reduce the systemic inflammation in participants with HFmrEF or HFpEF and thereby possibly improve their HF-related symptoms, morbidity and mortality, physical function, health-related quality of life (HRQoL), providing further benefits to ziltivekimab-treated participants in the study.

All participants in this study will receive study intervention and auxiliary supplies free of charge.

2.3.3 Overall benefit-risk conclusion

Blocking IL-6 for anti-inflammatory benefits is not a curative intervention, and prolonged or chronic treatment is usually needed to suppress the underlying pathology. This fact accentuates that IL-6 blockade should ideally be done in a way that does not lead to increased susceptibility to infections or other adverse side effects. Avoiding interfering with the pivotal homeostatic controls exercised by IL-6 also needs to be balanced against the level of anti-inflammation needed for adequate disease management. Data from the clinical development programme for ziltivekimab has not revealed any safety issues that would outweigh the benefits.[9] This is supported by the acceptable safety and tolerability profile observed for other anti-IL-6 receptor and anti-IL-6 therapies.

The study population will consist of participants with HFmrEF or HFpEF and systemic inflammation. Assessment of risk factors and appropriate attention to the standard of care treatment will be ensured throughout the study. As the study will include a vulnerable population, relevant precautions for the study intervention have been implemented in the design and planned conduct of the study to minimise the risks and inconveniences of participating in the study.

Taking into account the measures taken to minimise risk and burden to participants in this study, the potential risks identified in association with ziltivekimab are justified by the anticipated benefits that may be afforded to participants with HFmrEF or HFpEF and systemic inflammation. Furthermore, for placebo-treated participants, the potential benefits from the study will outweigh the potential risks.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of ziltivekimab may be found in the current version of the ziltivekimab investigator's brochure[9] and any updates thereof.

3 Objectives, endpoints and estimands

3.1 Objectives and endpoints

Study objectives and endpoints are summarised in Table 3-1.

Table 3-1 Objectives and endpoints

Objectives	**Endpoints**		
Primary	**Title**	**Time frame**	**Unit**
To demonstrate the superiority of ziltivekimab 15 mg s.c. once-monthly versus placebo, both added to standard of care, in reducing the risk of CV death and HF events in participants with HFmrEF or HFpEF and systemic inflammation.	*Primary*		
	Time to first occurrence of a composite HF endpoint consisting of: • CV death[a,b] • HF hospitalisation[a] or urgent HF visit[a]	From randomisation (month 0) to end of study (up to 48 months[c])	Months
	Confirmatory secondary		
	Number of CV deaths[a,b], HF hospitalisations[a] or urgent HF visits[a] (first and recurrent)	From randomisation (month 0) to end of study (up to 48 months[c])	Count of event
Secondary	**Title**	**Time frame**	**Unit**
To demonstrate the superiority of ziltivekimab 15 mg s.c. once-monthly versus placebo, both added to standard of care, in reducing the risk of expanded composite HF endpoint in participants with HFmrEF or HFpEF and systemic inflammation.	*Confirmatory secondary*		
	Time to first occurrence of 4-point expanded composite HF endpoint, a composite endpoint consisting of: • CV death[a,b] • HF hospitalisation[a] or urgent HF visit[a] • Non-fatal MI • Non-fatal stroke	From randomisation (month 0) to end of study (up to 48 months[c])	Months
	Supportive secondary		
	Time to first occurrence of 4-point expanded composite HF endpoint, a composite endpoint consisting of: • All-cause death[a,b] • HF hospitalisation[a] or urgent HF visit[a] • Non-fatal MI • Non-fatal stroke	From randomisation (month 0) to end of study (up to 48 months[c])	Months
To demonstrate the superiority of ziltivekimab 15 mg s.c. once-monthly versus placebo, both added to standard of care, in reducing the risk of death in participants with HFmrEF or HFpEF and systemic inflammation.	*Confirmatory secondary*		
	Time to occurrence of CV death[a,b]	From randomisation (month 0) to end of study (up to 48 months[c])	Months
	Time to occurrence of all-cause death[a,b]	From randomisation (month 0) to end of study (up to 48 months[c])	Months
To compare the effects of ziltivekimab 15 mg s.c. once-monthly versus placebo, both added to standard of care, in improving the overall clinical	*Supportive secondary*		
	Hierarchical composite of: Time to all-cause death[a,b], number of HF hospitalisatiosn[a] or urgent HF visits[a],	From randomisation (month 0) to end of study (up to 48 months[c])	Total wins for each

Objectives	Endpoints		
benefit of participants with HFmrEF or HFpEF and systemic inflammation.	time to first HF hospitalisation[a] or urgent HF visit[a], difference of at least 5 in KCCQ clinical summary score change from baseline to 12 months (assessed by the win ratio).		treatment group
To compare the effects of ziltivekimab 15 mg s.c. once-monthly versus placebo, both added to standard of care, in reducing the risk of HF events in participants with HFmrEF or HFpEF and systemic inflammation.	*Supportive secondary*		
	Time to first occurrence of HF hospitalisation[a] or urgent HF visit[a]	From randomisation (month 0) to end of study (up to 48 months[c])	Months
To compare the effects of ziltivekimab 15 mg s.c. once-monthly versus placebo, both added to standard of care, in reducing the risk of atrial fibrillation (AF) events in participants with HFmrEF or HFpEF and systemic inflammation.	*Supportive secondary*		
	Number of events of atrial fibrillation	From randomisation (month 0) to end of study (up to 48 months[c])	Count
To compare the effects of ziltivekimab 15 mg s.c. once-monthly versus placebo, both added to standard of care, in improving the health status of participants with HFmrEF or HFpEF and systemic inflammation.	*Supportive secondary*		
	Change in KCCQ clinical summary score	From randomisation (month 0) to 12 months	Score (no unit, range; 0-100)
	Improvement of 5 points or more in KCCQ clinical summary score (yes/no)	From randomisation (month 0) to 12 months	Count of participant
	Improvement of 10 points or more in KCCQ clinical summary score (yes/no)	From randomisation (month 0) to 12 months	Count of participant
	Improvement in NYHA Class (yes/no)	From randomisation (month 0) to 12 months	Count of participant
To compare the effects of ziltivekimab 15 mg s.c. once-monthly versus placebo, both added to standard of care, on progression of CKD in participants with HFmrEF or HFpEF, systemic inflammation.	*Supportive secondary*		

	Time to first occurrence of a composite CKD endpoint consisting of:
	• CV death[a,b]
	• onset of persistent[d] ≥ 40% reduction in eGFR (CKD-EPI[10]) compared with baseline
	• kidney failure defined as:
	  • death from kidney failure[a, e]
	  • onset of persistent[d] eGFR< 15 mL/min/1.73 m^2 (CKD-EPI[10])
	  • initiation of chronic kidney replacement therapy (maintenance dialysis or kidney transplantation)
		From randomisation (month 0) to end of study (up to 48 months[c])	Months

	Change in eGFR (CKD-EPI[10])	From randomisation (month 0) to 12 months	mL/min/ 1.73 m^2
	Annual rate of change in eGFR (CKD-EPI[10]) (total eGFR slope)	From randomisation (month 0) to end of study (up to 48 months[c])	mL/min/ 1.73 m^2/ year

Objectives	Endpoints		
To compare the effects of ziltivekimab 15 mg s.c. once-monthly versus placebo, both added to standard of care, in participants with HFmrEF or HFpEF and systemic inflammation, on risk of severe infections	*Supportive secondary*		
	Number of hospitalisations with infection as primary cause[a] or death due to infection[a]	From randomisation (month 0) to end of study (up to 48 months[c])	Count of event
To compare the effects of ziltivekimab versus placebo on biomarkers of inflammation, HF and anaemia in participants with HFmrEF or HFpEF and systemic inflammation	*Supportive secondary*		
	Change in hs-CRP	From randomisation (month 0) to 12 months	Ratio to baseline
	Change in NT-proBNP	From randomisation (month 0) to 12 months	Ratio to baseline
	Exploratory		
	Change in haemoglobin	From randomisation (month 0) to 12 months	Ratio to baseline

Notes:
[a] Based on EAC-confirmed events;
[b] including undetermined cause of death;
[c] Maximum treatment duration is dependent on event rates and is estimated to be approximately 48 months including a 3-month follow-up period;
[d] "Persistent" is defined as 2 consecutive samples meeting the criteria. The 2 samples must be at least 4 weeks apart;
[e] Defined as a non-CV death that is due to the direct consequences of severely impaired kidney function.
Abbreviations: CKD = chronic kidney disease; CV = cardiovascular; EAC = event adjudication committee; eGFR = estimated glomerular filtration rate; HF = heart failure; HF events = HF hospitalisations and urgent HF failure visits; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; hs-CRP = high-sensitivity C-reactive protein; KCCQ = Kansas City Cardiomyopathy Questionnaire; MI = myocardial infarction; NT-proBNP = N-terminal-pro-brain natriuretic peptide; NYHA = New York Heart Association (classification); s.c. = subcutaneous.

Local requirements may apply. China: see country/region-specific requirements (Appendix 11, Section 10.11).

3.2 Estimands

Primary estimand

The primary clinical question is: What is the treatment effect of ziltivekimab 15 mg s.c. once-monthly vs placebo, both added to standard of care, on time to first occurrence of either CV death or HF hospitalisation or urgent HF visit for patients with HFmrEF or HFpEF and systemic inflammation, irrespective of treatment discontinuation or treatment pauses for any reason, changes to CV risk lowering background medication, coronary revascularisation, or device implantation while the patient is alive (i.e., have not had a non-CV death)?

The primary estimand is defined with the five attributes as defined in ICH E9(R1) addendum[44]:

- Treatment condition: The treatment regimen evaluated is ziltivekimab 15 mg s.c. once-monthly vs placebo, both added to standard of care, irrespective of treatment discontinuation or treatment pauses for any reason, changes to CV risk lowering background medication, coronary revascularisation and device implantation (treatment policy strategy).

- Population: Patients with HFmrEF or HFpEF with preserved ejection fraction and systemic inflammation.
- Variable/endpoint: Time to first occurrence of the primary composite, observed from randomisation to end of study.
- Remaining intercurrent events: Deaths from non-CV causes are handled by the while-alive strategy. Other intercurrent events are addressed in the treatment condition attribute.
- Population-level summary: The hazard ratio between treatment conditions.

Results based on the primary estimand quantifies the achievable treatment effect regardless of other concomitant CV treatment and regardless of adherence to randomised treatment. This is considered relevant to include in an intention-to-treat evaluation of the primary objective. Handling of non-CV deaths by the while-alive strategy is considered reasonable, as the rate is expected to be the same for the two treatment conditions.

Secondary estimands

The treatment effect of ziltivekimab 15 mg s.c. once-monthly vs placebo, both added to standard of care on confirmatory secondary endpoints will be estimated to address secondary objectives.

In the estimands for the confirmatory secondary objectives, the treatment condition and population are the same as for the primary estimand. For the confirmatory secondary time-to-event endpoints, the variable is time to first occurrence of the endpoint event, observed from randomisation to end of study, and the population-level summary is the hazard ratio between treatment conditions. For the HF endpoint, the variable is the number of HF events (HF hospitalisations and urgent HF visits), observed from randomisation to end of study, and the population-level summary is the ratio of the mean number of events between treatment conditions. The remaining intercurrent events are the causes of death not part of the specific variable (endpoint) handled by the while-alive strategy.

4 Study design

4.1 Overall design

This is an interventional, randomised, parallel-group, double-blind, placebo-controlled, multi-centre, multi-national cardiovascular outcomes trial (CVOT) designed to evaluate the effects of ziltivekimab 15 mg versus placebo (randomised 1:1), both administered s.c. once-monthly and added to standard of care, on morbidity and mortality of participants with HFmrEF or HFpEF and systemic inflammation.

The study is event-driven, with study closure being performed when the targeted number of primary endpoint events has been reached. The study will employ a group sequential design and interim testing will be evaluated by an independent external data monitoring committee (DMC). The timing and rules applied in the interim analysis will be prespecified.

The recruitment period is anticipated to be approximately 36 months, and with the assumed event rate, the expected study duration is approximately 4 years. Note that the recruitment period in China may be extended beyond 36 months from global FPFV due to the relative longer study initiation timeline and participant recruitment challenges; please see Appendix 11 (Section 10.11).

The sample size and expected duration of the study are based on assumptions of event rate of the primary endpoint (time to first CV-death or HF event).

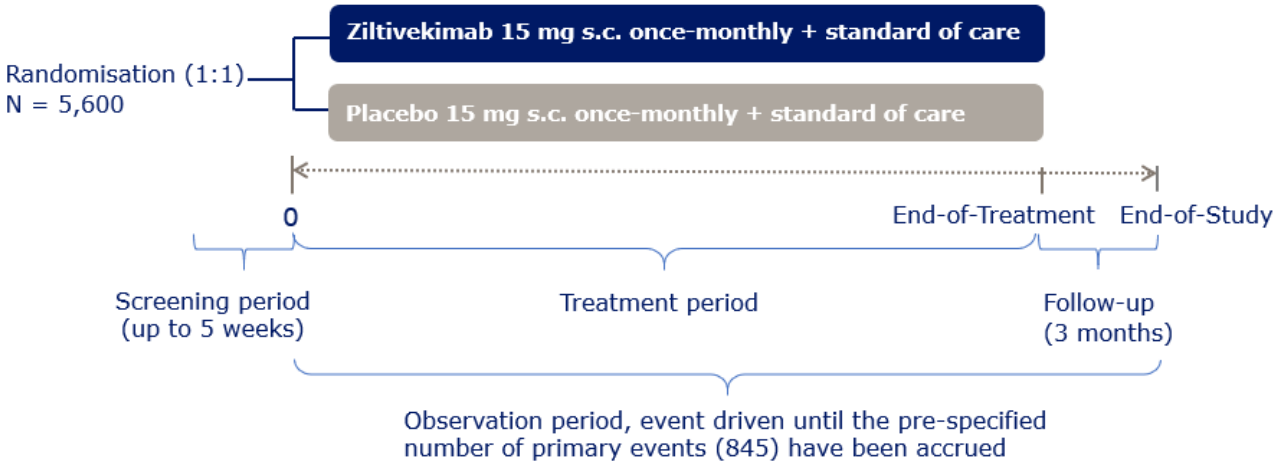
Participants are expected to stay in the study for the complete duration of the study. Hence, participants will be followed for the complete duration of the study irrespective of their adherence to randomised study intervention or adherence to the protocol in general. Extensive efforts must be made to keep the participants on study intervention (see Section 6.4.2 for details). However, in case of a potential safety concern, unacceptable intolerability or at the request of the participant, the study intervention may be discontinued (see Section 7 for details). Participants should be encouraged to stay in the study irrespective of the degree of adherence to randomised treatment (investigational medical product). Furthermore, diligent and extensive efforts should be made to collect outcome data on all randomised participants including those who discontinued treatment early.

The study consists of 3 periods: a screening period (up to 5 weeks), the treatment period and a 3-month follow-up period after the end of treatment visit. The total study duration for an individual participant is estimated to be up to 4 years, depending on when the participant is enrolled.
A schematic overview of the study is provided in Figure 4-1 below.

An external event adjudication committee (EAC) will perform ongoing adjudication of predefined events in an independent and blinded manner for evaluation of the primary endpoint and secondary safety endpoint (Table 8-1).

An independent DMC will monitor the safety of participants enrolled in the study (see Appendix 1, Section 10.1.6.2 for details).

Figure 4-1 Study design



4.2 Scientific rationale for study design

The study has been designed in accordance with the requirements for adequate and well-controlled studies.[45]

The potential risk of infections with ziltivekimab is considered acceptable from an ethical perspective in the present study population based on the significant unmet medical need. The safety of the participants will be carefully monitored throughout the study, from the screening visit to the end of study visit. Conditions and events occurring prior to initial dose of study intervention will be recorded as medical history, whereas conditions and events with onset after the initial dose will be recorded as adverse events if fulfilling the predefined criteria. Furthermore, an external and independent DMC will monitor the safety of participants enrolled in the study.

Established standard of care therapies will be provided throughout the study, therefore, assignment to placebo will not place participants at any increased risk. A special focus will be on managing the risk of infections in the study. A broad spectrum of concomitant treatment including any and all appropriate treatment for HF or treatment of any other medical condition or comorbidity, can be introduced, altered or adjusted throughout the study based on individual requirements and at investigator's discretion. This is in accordance with a pragmatic approach to compare two treatment regimens; one where ziltivekimab is available and another where it is not.

The study design and visit schedule is optimised to enhance treatment adherence and participant retention in the study. To support participants during the initiation of treatment and for closer safety monitoring, site contacts will occur more frequently (i.e., monthly) during the first 3 months of the study.

The study is designed as a 2-armed study (ziltivekimab and placebo) in accordance with the study objectives and to minimise bias in the results. Randomised and double-blinded treatment with ziltivekimab or placebo offers a robust method for assessment of the effects of ziltivekimab. Furthermore, as the study includes endpoints that can be influenced by expectation bias or motivation (i.e., patient reported outcomes), blinding of investigators and participants is critically important.

The comparison to placebo is chosen to ensure the scientific rigour of the study. The placebo control will facilitate evaluation of the efficacy as well as the safety and tolerability of ziltivekimab by allowing adverse events associated with ziltivekimab to be distinguished from symptoms of the underlying disease.

The up to 4-year treatment period will allow sufficient time to observe and evaluate reduction in systemic inflammation, morbidity and mortality with ziltivekimab in participants with HFmrEF or HFpEF and systemic inflammation and to evaluate safety, also uncovering potential sustained effects after stopping study intervention. Based on the half-life of ziltivekimab, a 3-month follow-up period after end of treatment is considered sufficient in length to ensure follow-up for the duration of recovery of blood parameters and evaluation of potential withdrawal effects, while balancing study feasibility such as participant retention in the off-drug follow-up period.

A multinational design has been chosen to ensure a sufficient screening pool of potential study participants and to reflect the anticipated patient population. The study will include a population of participants with HFmrEF or HFpEF and systemic inflammation (Section 5) which is an appropriate target population for an intervention aiming at showing reductions in systemic inflammation. The eligibility criteria are sufficiently broad to cover the continuum of HFmrEF and HFpEF and allow enrolment of a clinically relevant subpopulation, while at the same time excluding participants unlikely to complete the study due to pre-existing severe clinical conditions.

The study population represents a broad HFmrEF and HFpEF population with elevated NT-proBNP and structural and/or functional echocardiographic findings in line with previous trials and guidelines.[2, 3] The guidelines[2, 3, 46] arbitrarily categorise HF with LVEF 41 to 49% as HF with mildly reduced EF (HFmrEF), and reserves HFpEF for LVEF above or equal to 50%. The inclusion of patients with HFmrEF is based on similar pathophysiological considerations where lowering inflammation is expected to improve several of the factors driving the progression of HF despite the systolic function remaining to be mildly reduced. Elevated hs-CRP is added to focus on a phenotype with systemic inflammation.[47] The population included in the study represents an enriched, high-risk population in order to increase event rates of the primary outcomes and thereby to ensure that the secondary objectives of the study can be evaluated within a reasonable timeframe and sample size. The population has been enriched by inclusion of patients with highly elevated NT-proBNP or with elevated NT-proBNP in combination with a recent HF hospitalisation or urgent/unplanned visit due to decompensated HF which required intravenous (i.v.) loop diuretic treatment within the previous 9 months (inclusion criterion #4).

In general, a decrease in mortality provides evidence of effectiveness in HF and is considered a hard endpoint. CV death and all-cause death are included as components in the composite endpoints and have been specified as stand-alone ‘time to event’ confirmatory endpoints.

Furthermore, HF hospitalisations represent an important clinical outcome, reflecting worsening function and/or symptoms, interruption of daily activities, and superimposed risks and inconveniences. As HF treatment, in some countries, moves away from the in-patient setting, the component ‘urgent HF visits’ is included in the HF endpoint as these visits reflect clinically important worsening symptoms leading to an intervention. Hence, the HF endpoint consists of HF hospitalisation and urgent HF visit. The HF endpoint is included as a measure of morbidity both as a component of a composite HF outcomes endpoint that includes mortality and as an independent

endpoint. The endpoints (composite HF endpoint and HF events) are assessed as 'time-to-first event'. The composite HF endpoint is also assessed as total number of events, i.e., including both first and recurrent HF events.

The expanded composite HF endpoint include HF events (HF hospitalisation or urgent HF visit) in addition to the components in the traditional 3-point MACE (CV-death, non-fatal MI and non-fatal stroke).

An external independent event adjudication committee (EAC) will be constituted to adjudicate predefined events in an independent and blinded manner; the EAC will have no mandate to impact study conduct, study protocol or amendments. The primary endpoint will be based on EAC-confirmed events. The individual components of the primary endpoint (HF events and death including CV-death) will be adjudicated according to the standards as defined in 'Cardiovascular and Stroke Endpoint Definitions for Clinical Trials' as defined by the Standardized Data Collection for Cardiovascular Trials Initiative (SCTI).[48]

Events of non-fatal myocardial infarction and stroke, components of secondary endpoints, will be based on investigator reported events. Hence, only for the primary endpoint, all individual components will be adjudicated. This is to form the basis for a firm conclusions. Furthermore, HF events are difficult to obtain with similar accuracy across sites and countries. A higher degree of consensus is expected on the myocardial infarction and stroke events to be reported by the investigator.

Furthermore, infections of special interest will be adjudicated by the EAC to identify hospitalisations with infection as primary cause or death due to infection, and thereby systematically assess and closely monitor, that ziltivekimab does not increase the risk of severe infections.

An objective related to kidney function is also included to evaluate the effects of reduced inflammation with ziltivekimab on the progression of CKD, which is present in 30-50% of patients with HFmrEF and HFpEF.[49] There is a close interplay and mutual dependency between HFpEF and CKD, and the risk of adverse outcomes and mortality increases with more advanced CKD.[32] As such, an improvement in kidney function or a slowed progression of CKD will likely benefit the condition and outcomes of HFmrEF and HFpEF.

Atrial fibrillation (AF) and HFmrEF and HFpEF are closely related.[50] One can lead to the other. Inflammation plays a central role in the pathophysiology. In HFpEF and HFmrEF, increased filling pressure cause left atrial dilatation which triggers AF. Lowering inflammation with ziltivekimab, may lower left ventricular filling pressure which may lead to a decrease in left atrial (LA) size and AF occurrence. Hence, a secondary objective related to evaluation of the risk of AF events in participants with HFmrEF or HFpEF and systemic inflammation is included.

Increased cardiac filling pressure generally leads to elevation of NT-proBNP and BNP due to increased ventricular wall tension[51], changes in NT-proBNP has been included as a supportive endpoint in the study as a biomarker on the effect of ziltivekimab on HF.

The safety of the participants will be monitored closely throughout the study with specific focus on potential risks of ziltivekimab, the patient population included in the study and the endpoints defined for the study (Sections 8.2 and 8.3).

Ziltivekimab serum concentration data will be obtained to evaluate the effects of prespecified covariates on serum concentrations of ziltivekimab using a population PK analysis. The sampling times included in the current study (i.e., at baseline, 1, 3 and 6 months post initial dose, at every 6 months during the study, at EoT and EoS), will allow for comparison of the pharmacokinetic profile of ziltivekimab in patients with HFmrEF or HFpEF and systemic inflammation with the pharmacokinetic profile obtained in Caucasian, Japanese and Chinese patients with CKD and systemic inflammation.

4.2.1 Patient input into design

Patients reflecting the ziltivekimab target population have given input to the flexibility and patient-centricity of the study design and visit schedule. The patients have also given input to printed materials for the education and information of participants. These materials have been developed to support participants' understanding and awareness about their health, and for discussion with their caregivers.

Furthermore, a study app has been developed together with patients which enables the patient voice to be integrated into the conduct of the study and to anticipate and remove barriers to ensure the best possible outcomes for participants' clinical study experience.

4.2.2 Input to study design from supportive panels

Investigators, study nurses and study coordinators with experience with the target patient population and in conduct of CVOTs have been involved in evaluating the inclusion/exclusion criteria and assessments in the protocol and in developing materials and resources for participants and their caregivers. This input has contributed to clarifying the definitions and easing the operational aspects for participants and sites and to ensuring participant understanding of the materials and resources.

Furthermore, the steering committee (StC) including key opinion leaders, and regulatory agencies (including the FDA and the Committee for Medicinal Products for Human Use at the European Medicines Agency) have been consulted for their input to the study design, inclusion/exclusion criteria and assessments.

4.3 Justification for dose

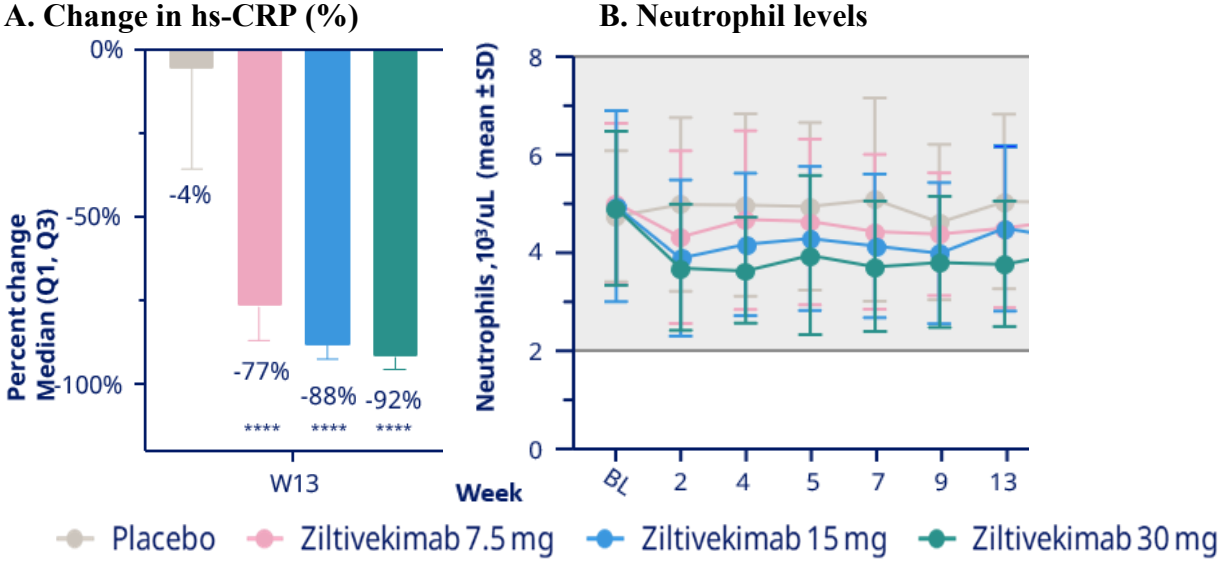
Ziltivekimab is a human monoclonal antibody directed against IL-6 ligand, with extended half-life technology; the estimated half-life is 57 days, making it suitable for once-monthly administration.[9] A phase 2 dose finding study with ziltivekimab, denoted RESCUE-US, was designed to enable the selection of an adequate dose to be studied in the cardiovascular outcomes trial (CVOT) with ziltivekimab in patients with ASCVD, CKD and systemic inflammation (details are provided in current version of the ziltivekimab investigator's brochure[9] and any updates thereof). Participants with CKD and systemic inflammation (serum hs-CRP level ≥2.0 mg/L) were randomised to one of three dose levels of s.c. ziltivekimab (7.5 mg, 15 mg and 30 mg every four weeks [Q4W]) or placebo. Ziltivekimab demonstrated robust, sustained and dose-dependent reduction of systemic inflammation, observed as median reductions in hs-CRP levels of 77%, 88% and 92%, respectively,

after 12 weeks of treatment (week 13 visit) (Figure 4-2). In an exposure response analysis, a consistent decrease in hs-CRP was observed across the exposure range for the ziltivekimab 15 mg dose. In addition, decreases in other inflammatory markers (fibrinogen, serum amyloid A and haptoglobin) were observed at all dose levels.

Ziltivekimab was well tolerated. Small, dose-dependent decreases in neutrophils and platelets were observed.[9] Decreases in neutrophils were not associated with adverse events of infection and decreases in platelets were not associated with adverse events of bleeding. Furthermore, levels of LDL-cholesterol, triglycerides and apolipoprotein B modestly increased with ziltivekimab; increases were most pronounced with ziltivekimab 30 mg Q4W. However, levels of HDL-cholesterol and apolipoprotein A were increased with ziltivekimab, and therefore no change in atherogenic lipid ratios were observed. Elevations in liver enzymes (AST/ALT) were marginal and not clinically relevant. No allergic injection site reactions were reported; one event of injection site pain was reported with 15 mg ziltivekimab.

The ziltivekimab 15 mg once-monthly dose was selected for the CVOT as this dose level was associated with a near maximal effect on the efficacy biomarker (hs-CRP), while limiting the effect on safety-related biomarkers, in particular neutrophil and platelet counts. The effect of doubling the ziltivekimab dose from 15 to 30 mg was marginal on hs-CRP reduction, while the effects on neutrophils with the inherent infection risk increased with increasing dose (Figure 4-2).

Figure 4-2 Dose-dependent effects of ziltivekimab on change in hs-CRP levels (panel A) and neutrophil levels (panel B) during initial 12 weeks of treatment (week 13 visit) – RESCUE-US



Note: Study intervention was administered at weeks 1, 5, 9, 13, 17, and 21; **** $p < .0001$.
Abbreviations: BL = baseline; W13 = week 13 visit after 12 weeks of treatment.

Any favourable effects of ziltivekimab 15 mg on IL-6 and hs-CRP levels and ziltivekimab safety profile observed in patients with CKD will likely also be applicable for a HFmrEF and HFpEF population.

Data from the subset of participants with HF included in RESCUE-US support the selection of ziltivekimab 15 mg for treatment of patients with HFmrEF or HFpEF. A total of 31 participants

included in RESCUE-US had HF at baseline as defined by medical history of 'cardiac failure congestive' (MedDRA term). Although based on a small subset of the population, a dose-dependent reduction of systemic inflammation was evident among participants with HF; observed as median reductions in hs-CRP levels of 81%, 84% and 90% with ziltivekimab 7.5 mg, 15 mg and 30 mg respectively, as compared to 18% with placebo, after 12 weeks of treatment (week 13 visit).

Based on the similar effect on hs-CRP in the total RESCUE-US population and in RESCUE-US patients with HF, the effects of ziltivekimab are assumed not to be different in patients with HFmrEF or HFpEF and systemic inflammation. Hence, the ziltivekimab 15 mg once-monthly dose selected for the ZEUS CVOT is also applicable for this study.

4.4 End of study definition

The end of the study is defined as the date of the last visit of the last participant in the study globally.

A participant is considered to have completed the study if he/she has:

- attended the final scheduled visit (follow-up visit – V-EoS) according to the flowchart (Section 1.2) *or*
- died during study. 'Date of completion' is the day of death.

The study is event driven; therefore, end of treatment visit (V-EoT) and end of study (V-EoS) will be scheduled according to projected study closure. If the event rate is lower than anticipated, then visits and related assessments will be repeated every 3 months beyond V18 (at month 42) until the necessary number of primary outcome events have been accrued. When study closure is initiated, the investigators will be notified and instructed by Novo Nordisk regarding the visit schedules for their participants. Please note, that study closure may need to be performed in an expedited manner.

The Primary Completion Date (PCD) is defined as the date on which the last participant in the clinical study has an assessment for the primary endpoint, and for this study it is the last participant last visit (LPLV).

4.4.1 End of study assessments

When the study comes to an end, the investigator must make every effort to ascertain efficacy endpoint data and adverse events (AEs) with a focus on those related to the primary objective for all participants. This should be done at the scheduled V-EoT and V-EoS or by direct contact with the participant whenever possible. If a participant proves difficult to reach for the follow-up visit (V-EoS), all attempts to re-establish direct contact should be made as noted below. If establishing direct contact is not possible, AE status should be obtained from any available source including electronic medical records, the participants' primary physician or other health care professionals and, as a last resort, vital status (dead or alive) should be obtained. Publicly available data sources should also be searched. A search agency may be used to facilitate identifying updated contact details for a missing participant or provide vital status (dead or last alive date). The above suggestions should be followed unless prohibited by local regulation and may be modified according to practical aspects.

Local requirements may apply. Czech Republic, France, Portugal: see country/region-specific requirements (Appendix 11, Section 10.11).

In a case where several attempts are required to establish direct contact to a participant, it may be necessary to exceed the visit window of the follow-up visit (V-EoS). In order for the data set to be as complete as possible, end of study follow-up information can be collected until the randomisation codes are broken.

As a minimum the following contact attempts should be made and documented in the source documents:

- To participants: three phone calls and one written contact (certified letter to the participants' last known mailing address or local equivalent methods)
- To primary physician and/or other health care professionals: calls until contact is established
- To relatives or others on the contact persons list: three phone calls and one written contact
- Search/contact to public registries, if available and allowed by local regulation.

5 Study population

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

Pre-screening is defined as review of the patient medical records, including handing out participant information, as well as database review. Any pre-screening activities must be documented on site by the investigator.

5.1 Inclusion criteria

All inclusion criteria are based on the participants' medical records, except for inclusion criteria #3 (hs-CRP at central laboratory), #4 (NT-proBNP at central laboratory, and ECG assessed at screening) and #5 (NYHA class) assessed at screening (visit 1).

Local requirements may apply. China, Czech Republic, France, Germany, Hungary, Lithuania, Netherlands, Portugal, Singapore, South Korea, Spain, Taiwan: see country/region-specific requirements (Appendix 11, Section 10.11).

Participants are eligible to be included in the study only if all the following criteria apply:
General

1. Informed consent obtained before any study-related activities. Study-related activities are any procedures that are carried out as part of the study, including activities to determine suitability for the study.
2. Age 18 years or above at the time of signing the informed consent.
3. Serum hs-CRP ≥2 mg/L at screening (visit 1).[a]

Disease specific - cardiovascular

4. At least one of the following[a]:
    a. NT-proBNP ≥ 300 pg/mL at screening (Visit 1) for patients without ongoing atrial fibrillation/flutter. If ongoing atrial fibrillation/flutter at screening (visit 1), NT-proBNP must be ≥ 600 pg/mL.
    b. HF hospitalisation or urgent/unplanned visit with a primary diagnosis of decompensated heart failure which required intravenous loop diuretic treatment, within the last 9 months prior to screening (visit 1) *in combination with* NT-proBNP ≥ 200 pg/mL at screening (Visit 1) for patients without ongoing atrial fibrillation/flutter. If ongoing atrial fibrillation/flutter at screening (visit 1), NT-proBNP must be ≥ 600 pg/mL.
5. Diagnosis of heart failure (NYHA Class II-IV).
6. LVEF > 40% documented by echocardiography within 12 months prior to *or* at screening (visit 1). The LVEF must be documented in medical records and the most recent measurement must be used to determine eligibility with no interim event signalling potential deterioration in ejection fraction (e.g., MI or HF hospitalisation).
7. Structural heart disease *and/or* functional heart disease documented by echocardiography within 12 months prior to or at screening (visit 1) showing at least one of the following:
    - LA volume index > 34 mL/m^2.
    - LA diameter ≥ 3.8 cm.
    - LA length ≥ 5.0 cm.

- LA area ≥ 20 cm^2.
- LA volume ≥ 55 mL.
- Intraventricular septal thickness ≥1.1 cm.
- Posterior wall thickness ≥1.1 cm.
- LV mass index ≥115 g/m^2 in men or ≥ 95 g/m^2 in women.
- E/e' (mean septal and lateral) ≥ 10.
- e' (mean septal and lateral) < 9 cm/s.

8. No heart failure hospitalisations or urgent heart failure visits between screening (visit 1) and randomisation (visit 2).

[a] Patients participating in the prevalence study (NN6018-7527) may be enrolled based on the hs-CRP and/or NT-proBNP (requiring corresponding ECG from the same date) results obtained in the study, if no more than 90 days old.

Local requirements may apply. Germany, South Korea: see country/region-specific requirements (Appendix 11, Section 10.11).

5.2 Exclusion criteria

All exclusion criteria are based on the participants' medical records, except for exclusion criterion #3 (urine pregnancy test), criteria #9 to #12 and #27 (central laboratory tests), criteria #26 (central laboratory tests, if applicable), criterion #14 (blood pressure) and criterion #15 (ECG).

Local requirements may apply. Argentina, Austria, Belgium, Brazil, China, Czech Republic, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Latvia, Lithuania, Norway, Poland, Portugal, Romania, South Korea, Spain, Thailand, UK: see country/region-specific requirements (Appendix 11, Section 10.11).

Participants are excluded from the study if any of the following criteria apply:
General

1. Known or suspected hypersensitivity to study intervention or related products.
2. Previous randomisation in this study.
3. Female who is pregnant, breast-feeding or intends to become pregnant or is of childbearing potential and not using a highly effective contraceptive method, as defined in Appendix 4 (Section 10.4.2).
4. Participation (i.e., signed informed consent) in any other interventional clinical study of an approved or non-approved investigational medicinal product within 30 days prior to screening (visit 1).
5. Participation in any clinical study of an approved or non-approved device for the treatment of heart failure within 30 days prior to screening (visit 1).
6. Any disorder, which in the investigator's opinion might jeopardise participant's safety or compliance with the protocol.
7. Inadequate standard of care treatment which in the investigator's opinion makes participation in the study inappropriate.
8. Unstable medical therapy for heart failure (including dose of diuretics) within 14 days prior to screening visit (visit 1) (at the discretion of the investigator).

Laboratory values

9. Absolute neutrophil count <2×10^9/L at screening (visit 1).
10. Platelet count <120×10^9/L at screening (visit 1).
11. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2.5 × upper limit of normal at screening (visit 1).
12. Active hepatitis C (positive anti-HCV and detectable HCV RNA) or hepatitis B (positive HBsAg and/or positive anti-HBc with detectable HBV DNA) at screening (visit 1). (*Note: Participants with positive anti-HBc and undetectable HBV DNA can be enrolled; see Section 8.2.8 for details*).

Medical conditions – cardiovascular

13. Myocardial infarction, stroke, unstable angina pectoris, transient ischaemic attack, or heart failure hospitalisation within 30 days prior to screening (visit 1).
14. Systolic blood pressure ≥180 mmHg at screening (visit 1). If the systolic blood pressure is 160-179 mmHg, the patient should be receiving ≥3 antihypertensive drugs. *(Note: Potential participants may be retested for this criterion within the visit window and without rescreening, at the discretion of the investigator*).
15. Heart rate above 110 or below 40 beats per minute as evaluated on the ECG performed at screening (visit 1) *(Note: Potential participants may be retested for this criterion within the visit window and without rescreening, at the discretion of the investigator)*.
16. Planned coronary, carotid or peripheral artery revascularisation known during the screening period (visit 1). *(Note: planned coronary angiogram is not exclusionary)*.
17. Planned cardiac device or atrial flutter/atrial fibrillation ablation procedure known during the screening period (visit 1).
18. Major cardiac surgical, non-cardiac surgical, or major endoscopic procedure (thoracoscopic or laparoscopic) within the past 60 days prior to randomisation (visit 2) or any major surgical procedure planned at the time of randomisation (visit 2).
19. Left Ventricular Assist Device (LVAD) implantation or heart transplantation
20. Heart failure due to infiltrative cardiomyopathy (e.g., sarcoid, amyloid), arrhythmogenic right ventricular cardiomyopathy, Takutsubo cardiomyopathy, genetic hypertrophic cardiomyopathy or obstructive cardiomyopathy, active myocarditis, constrictive pericarditis, cardiac tamponade, uncorrected more than moderate primary valve disease.
21. Primary pulmonary hypertension, chronic pulmonary embolism, severe pulmonary disease including COPD.
22. Any other condition judged by the investigator that could account for heart failure symptoms and signs (e.g., anaemia, hypothyroidism).

Medical conditions – infections/immunosuppression

23. Clinical evidence of, or suspicion of, active infection at the discretion of the investigator.
24. History of recurrent serious infections (infections leading to hospitalisation or use of i.v. antibiotics) in the 12 months prior to randomisation (visit 2), at the discretion of the investigator.
25. Diagnosis of human immunodeficiency virus (HIV) and not receiving a stable antiretroviral regimen, at the discretion of the investigator at screening (visit 1).
26. History or evidence of untreated latent tuberculosis (TB) such as (but not limited to):
    - History of a positive TB test *or* chest X-ray compatible with latent TB; and TB treatment initiated less than 28 days prior to randomisation (visit 2).
    - Confirmed positive for latent TB at screening (visit 1) (see Section 8.2.7 for details) and TB treatment initiated less than 28 days prior to randomisation (visit 2).

Medical conditions - General health and safety

27. eGFR<15 mL/min/1.73 m^2 (CKD-EPI[10]) at screening (visit 1)[a]
    or
    chronic haemodialysis or peritoneal dialysis.
28. History of gastrointestinal perforation. (*Note: History of perforated appendicitis more than 5 years prior to screening (visit 1) is not exclusionary*).
29. History of active diverticulitis in the 5 years prior to randomisation (visit 2).
30. History of inflammatory bowel disease that has been clinically active during the 12 months prior to randomisation (visit 2).
31. Presence or history of malignant neoplasms or *in situ* carcinomas (other than basal or squamous cell skin cancer, low risk prostate cancer, or *in-situ* carcinomas of the cervix, or carcinoma *in situ*/high grade prostatic intraepithelial neoplasia (PIN)) within 5 years prior to screening (visit 1).
32. History of bone marrow or solid organ transplant or anticipated to receive an organ transplant during the study. *Note: Patients no longer receiving immune suppressant therapy and who are in full remission following bone marrow transplant can be included in the study.*

Prior or current medication

33. Received a live or attenuated-live vaccine product within 4 weeks of study intervention administration (visit 2) or expected to receive a live or attenuated-live vaccine product during the treatment period. (*Note: Not-live and not attenuated-live vaccines are not exclusionary. For guidance refer to Appendix 9, Section 10.9*).
34. Use of preventive systemic antibiotics, systemic antivirals, or systemic antifungals at screening (visit 1). (*Note: "Systemic" is defined as oral or i.v. administered drugs that are absorbed into the circulation. Antibiotics used to treat latent TB are exempted*).
35. Use of systemic immunosuppressive drugs (both small molecules and biologics) or disease modifying anti-rheumatic drugs (DMARDs including both biologic DMARDs like anti-TNF-alpha and conventional DMARDs like methotrexate) at screening (visit 1) or anticipated chronic use of such drugs any time during the study. (*Note: Use of otic, ophthalmic, inhaled, and topical corticosteroids or local corticosteroid injections are not exclusionary*).
36. Use of anti-IL-6 products at screening (visit 1) or anticipated use of such drugs any time during the study.

[a] Patients participating in the prevalence study (NN6018-7527) may be enrolled based on the eGFR results obtained in the study, if no more than 90 days old. Local requirements may apply. Germany: see country/region-specific requirements (Appendix 11, Section 10.11).

5.3 Lifestyle considerations

There are no restrictions to lifestyle in the study.

5.4 Screen failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently eligible for participation according to the inclusion/exclusion criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet requirements from regulatory authorities. Minimal information includes informed consent date, demography, screen failure details and eligibility criteria.

A screen failure must be registered in the RTSM/IWRS. If participants withdraw their consent prior to randomisation or do not return for randomisation a screen failure session must be made in the RTSM/IWRS. The reason for failure will in all cases be captured in the electronic case report forms (eCRF).

Individuals who do not meet the criteria for participation in this study may be rescreened in case the investigator assesses that potential changeable or fluctuating in- or exclusion criteria may have changed, e.g., biochemical parameters (hs-CRP, NT-proBNP, eGFR), HF hospitalisation or urgent HF visits between visit 1 and 2, or change in concomitant medication. Previously randomised participants cannot be re-screened.

Individuals who are rescreened are required to sign a new informed consent form and provided with a new subject ID. Rescreening must be registered in the RTSM/IWRS.

5.5 Run-in criteria and/or randomisation criteria and/or dosing day criteria

No specific criteria are defined. Potential participants must be eligible for the study based on the in- and exclusion criteria (Sections 5.1 and 5.2) prior to randomisation. First dose must only be administered after assessments related to primary and secondary endpoints are completed (Section 8).

5.6 Assessment of eligibility

It is the responsibility of the investigator to have sufficient evidence to ensure eligibility. If a potential participant is not from the investigators practice, reasonable efforts must be made to obtain a copy of the medical records for a potential participant from relevant party e.g., the primary physician and hospitals. It is at the investigator's discretion on a case-by-case basis to decide if the complete medical records are needed or if the available documentation is enough to determine whether a potential participant is eligible. The values used to assess eligibility must reflect the current health status of the potential participant.

Potential participants who do not fully meet eligibility (inclusion/exclusion) criteria must not be randomised. If a potential participant is randomised in error this will be handled as an important protocol deviation and the IRB/IEC and regulatory authorities must be notified according to local requirements. If there are no safety concerns, treatment with study intervention can be continued or resumed at the discretion of the investigator after a discussion with a Novo Nordisk medical expert.

Local requirements may apply. China, UK: see country/region-specific requirements (Appendix 11, Section 10.11).

6 Study interventions and concomitant therapy

6.1 Study interventions administered

Study interventions include the investigational medical product, and the term 'study intervention' is used throughout the protocol to describe the intervention including the trial product.

6.1.1 Investigational medicinal products

Table 6-1 provides an overview of the study interventions (investigational medicinal products). Study interventions are provided by Novo Nordisk.

The study interventions are packed blinded and are visually identical.

Table 6-1 Study interventions

Study intervention name	Ziltivekimab 15 mg/mL	Ziltivekimab placebo
Dosage form	Solution for injection	Solution for injection
Route of administration	Subcutaneous	Subcutaneous
Dosage level	15 mg	0 mg
Dosing instructions	Once-monthly	Once-monthly
Formulation	B	-
Packaging/Delivery device	Single-use prefilled manual syringe (1 mL)	Single-use prefilled manual syringe (1 mL)

6.1.2 Administration of study interventions

All baseline assessments must be done prior to administration of the first dose of study intervention.

Only participants enrolled in the study may use study intervention.

Participants or caregivers will be instructed to inject the study intervention once-monthly. The injection can be administered at any time of the day irrespective of meals, but on the same day (date) of the month. The day of monthly administration can be changed, if necessary, as long as the time between two doses is at least 28 days and no longer than 2 weeks after the originally scheduled administration. If a dose is missed within 2 weeks from the scheduled administration, this dose should be administered as soon as it is discovered. If 2 or more weeks have gone, the participant should not take the missed dose but should await the next scheduled administration.

Information regarding the use of the prefilled syringe is available in the Directions for use (DFU) document. Furthermore, an instruction video of a patient taking the study intervention will be included in the study app. Injections are to be performed s.c. in a lifted skinfold in the abdomen, thigh, or upper arm. The date, time and site of injection (abdomen, thigh, or upper arm) of each dose administered will be recorded in the study app.

Training in DFU is the responsibility of the investigator or a delegate. The investigator must document that DFU was given to the participants verbally and in writing as a DFU document at the first dispensing visit and thereafter as needed during the study (as specified in the flowchart, Section 1.2). Moreover, the participants or caregivers must be trained in handling the injection when dispensed the first time and thereafter as indicated in the flowchart (Section 1.2) and as

needed during the study in order to ensure correct study intervention administration. Furthermore, the initial administrations of study intervention are to be performed by the participant or caregivers during the study visit, as indicated in the flowchart (Section 1.2), and the participants or caregivers should be observed by the investigator for correct administration of study intervention.

6.1.3 Other study supplies including non-investigational medical device

Participants who do not have a suitable smartphone will be provided with a device on which the study app has been preloaded.

Local requirements may apply: Portugal: see country/region-specific requirements (Appendix 11, Section 10.11).

6.2 Preparation, handling, storage and accountability

Local requirements may apply. Japan: see country/region-specific requirements (Appendix 11, Section 10.11).

6.2.1 Dispensing of study intervention administration

Each study site will be supplied with sufficient study interventions for the study on an on-going basis according to recruitment and randomisation.

Only delegated site staff may supply study intervention.

The initial administrations of study intervention are to be performed during the study visit, as indicated in the flowchart (Section 1.2). Study intervention will be dispensed to the participants at relevant visits for the remaining treatment period (see flowchart, Section 1.2).

If a participant is unable to attend the site for a dispensing visit (see flowchart in Section 1.2), a non-participating person may, however, collect the allocated study intervention on behalf of the participant. If study intervention is collected by a non-participant, this must be agreed with the participant on beforehand and thoroughly documented at the site e.g., by means of a letter of authorisation issued by the participant, and, on each occasion, the investigator must follow up by contacting the participant. Local requirements may apply. South Korea: see country/region-specific requirements (Appendix 11, Section 10.11).

In case a site visit is converted to a phone visit, or if study intervention cannot be dispensed to a participant during an on-site visit, the investigator may offer to send study interventions from the study site or pharmacy to the participant's home/residence/location by courier service. However, this option is only available for selected countries and if permitted by local regulations and can only be used as a last option to avoid treatment pauses. See Section 6.2.5 for further details and requirements. Local requirements may apply. Czech Republic, South Korea: see country/region-specific requirements (Appendix 11, Section 10.11).

In case local restrictions lead to lockdown of a site or pharmacy or a restriction of movement of participants, alternative ways of dispensing study intervention may be implemented, and details will be communicated and documented in alignment with Appendix 10 (Section 10.10). The dispensing

options will be based on options and requirements at country/region level and if permitted by local regulations.

6.2.2 Preparation of study intervention

The study intervention is provided in a ready-to-use prefilled syringe, i.e., no preparation is needed. Conditions for storage outside the refrigerator will be available on the label and in the Trial Materials Manual (TMM). For details regarding administration of study intervention please refer to Section 6.1.2.

6.2.3 Handling and storage of study intervention

Acceptable temperature ranges and conditions for storage and handling of each study intervention in- and outside the refrigerator are described in the Trial Materials Manual (TMM). The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

All study intervention must be stored in a secure, controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff. Product storage conditions will be available on the label and in the TMM.

The investigator must inform Novo Nordisk immediately if any study intervention has been stored outside specified conditions. The study intervention must not be dispensed to any participant before it has been evaluated and approved for further use by Novo Nordisk. Additional details regarding handling of temperature deviations can be found in the TMM.

The investigator or designee must instruct the participant on how to manage the time of storage of the dispensed products outside refrigerator.

6.2.4 Accountability of study intervention

The investigator or designee is responsible for study intervention accountability and record maintenance (i.e., receipt, accountability, and final disposition records). Drug accountability is performed by using the RTSM/IWRS and should also be recorded in a separate study intervention accountability log.

Participants must ensure that all used, and unused study intervention including empty packaging material is returned as instructed by the investigator. The investigator or designee must instruct the participant in what to return at next visit.

Used prefilled syringes are potentially hazardous materials that should be disposed of in a safe manner and therefore will not be retained for drug accountability purposes. Empty packaging will be used to perform accountability of used study intervention. Study sites will provide participants with a sharps container for disposal of used prefilled syringes. Participants should return the sharps containers to the study site at each visit for disposal using appropriate biohazard precautions.

All returned (used or un-used), expired or damaged study intervention (for technical complaint samples see Appendix 6, Section 10.6) must be stored separately from non-allocated study

intervention. No temperature monitoring is required. Non-allocated study intervention, including expired or damaged products, must be accounted by the site and reconciled by the monitor, as unused, at the latest at closure of the study site.

Destruction of study intervention can be performed on an ongoing basis and will be done according to local procedures after accountability is finalised by the site and reconciled by the monitor. Destruction of study intervention must be documented in the RTSM/IWRS.

Local requirements may apply: see country/region-specific requirements (Appendix 11, Section 10.11).

6.2.5 Shipment of study intervention to participant's home/residence/location

In case a site visit is converted to a phone visit, or if study intervention cannot be dispensed to a participant during an on-site visit, the investigator may offer to send study intervention and auxiliaries from the study site or pharmacy to the participant's home/residence/location by courier service. However, this option is only available for selected countries and if permitted by local regulations and should mainly be used to prevent unnecessary treatment pauses.

A separate informed consent form for direct shipment of study intervention to the participant must be signed before delivery of study intervention to the participants home/residence/location can be arranged (see Appendix 1, Section 10.1.3). Shipment of study intervention should be conducted in agreement with Novo Nordisk.

The process for sending study intervention from the study site or pharmacy to a participant's home is described in a separate document. This document contains detailed instructions for preparing packaging and setting up the pick-up of study intervention, handover of study intervention from the study site or pharmacy staff to the courier, required temperature monitoring of study intervention, delivery to and receipt of study intervention by the participant. The process for returning study intervention to the study site or pharmacy by courier is also described in the document.

Investigators, study site/pharmacy staff and participants who will be involved in shipment of study intervention to the participant's home/residence/location will be adequately trained in this process.

Local requirements may apply. Czech Republic, South Korea: see country/region-specific requirements (Appendix 11, Section 10.11).

6.3 Measures to minimise bias: Randomisation and blinding

Randomisation

All participants will be screened and centrally randomised using a RTSM/IWRS and assigned to the next available treatment according to randomisation schedule. Study intervention will be dispensed at the study visits summarised in the flowchart (Section 1.2).

At screening, each participant will be assigned a unique 7-digit subject ID which will remain the same throughout the study. Each site is assigned a 4-digit number and all subject IDs will start with the site number. Subject IDs must not be re-assigned.

Blinding

This is a double-blind study in which participants, care providers, investigators and outcome assessors are blinded to study intervention allocation. The study intervention containing the active drug and the placebo are visually identical and will be packed in a manner that maintains blinding.

To preserve the blinding of the study in the event of interim evaluation, only a minimum number of Novo Nordisk personnel are allowed to see the randomisation table and treatment assignments before the study is completed.

The RTSM/IWRS is used for blind-breaking. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' study intervention is warranted. The safety of the participant must always be the first consideration in making such a determination.

If the investigator decides that unblinding is warranted, the investigator may, at the investigators' discretion, contact the sponsor to discuss the situation prior to unblinding a participants' study intervention, unless this could delay emergency treatment of the participant.

If a participants' study intervention is unblinded in RTSM/IWRS, Novo Nordisk (Global Safety department) will be notified automatically via RTSM/IWRS. The date and reason that the blind was broken must be recorded in the source documentation. The person breaking the blind must print the blind break confirmation notification generated by the RTSM/IWRS, sign and date the document. If RTSM /IWRS is not accessible at the time of blind break, the RTSM/IWRS helpdesk should be contacted. Contact details are listed in Attachment I.

The participant should continue in the study after breaking the blind. Treatment with study intervention can be resumed if there are no safety concerns at the discretion of the investigator.

When the blind is broken, the study intervention allocation will be accessible to the investigator and the Novo Nordisk Global Safety department.

Study intervention allocation will also be accessible to the special laboratories responsible for PK (Section 8.4) and immunogenicity analyses.

6.4 Study intervention compliance

6.4.1 Adherence to study procedures

Throughout the study, the investigator will remind the participant to follow the study procedures and requirements to ensure participant compliance.

6.4.2 Adherence to study interventions

When participants self-administer study intervention at the site or at home, the date, time and site of injection (abdomen, thigh, or upper arm) of each dose administered should be recorded electronically by the participant using an app. Compliance with study intervention administration will be assessed and the assessment documented at each visit.

Treatment compliance will be assessed by monitoring of drug accountability and by discussing treatment compliance and dosing conditions with the participant. Treatment compliance is defined

as taking between 80%-120% of the planned yearly doses (corresponding to 10-14 doses per year), and not missing two or more consecutive doses. The investigator must assess the amount of study intervention returned, including both unused study intervention and empty packaging (as a surrogate for used study intervention), and compare to what was dispensed at the previous visit and, in case of discrepancies, question the participant.

If any suspicion of non-compliance arises, the site must enter into a dialogue with the participant, re-emphasising the importance of compliance and uncover barriers to compliance. This dialogue must be documented.

If the participant has been off treatment, continuation of study intervention should be encouraged if considered safe as per the investigator's discretion. Treatment start and stop dates must be recorded in the eCRF.

6.4.3 Adherence to standard of care

Investigators should ensure that participants are treated according to recommended standard of care for treatment of HF, cardiovascular conditions, CKD and infectious disease, as well as treatment to ensure glycaemic control in participants with T2D. Recommendations for this will be provided in guidance documents from the steering committee (StC) and global expert panel (GEP) during study conduct.

Surveillance of adherence to standard of care will be performed centrally by Novo Nordisk. For participants where standard of care is not achieved, investigators may be approached to discuss treatment options.

If allowed according to local regulation, Novo Nordisk may compensate parts of the cost of some concomitant medication used to ensure adequate standard of care. Brazil, Turkey: see country/region-specific requirements (Appendix 11, Section 10.11).

6.5 Dose modification

No dose modifications are allowed during the study. Randomised participants will initiate treatment with ziltivekimab 15 mg/placebo s.c. once-monthly. Study participants should remain on the ziltivekimab 15 mg dose level until the end of treatment visit (V-EoT); however, treatment pauses are allowed e.g., if treatment with study intervention is associated with unacceptable AEs or due to other circumstances (see Section 7 for details).

If study intervention is discontinued, participants should continue to follow the study schedule without being withdrawn from the study. Treatment with study intervention should be resumed if deemed safe at the discretion of the investigator.

6.6 Continued access to study intervention after end of study

When discontinuing study intervention at the end of the treatment period, the participant should be treated at the discretion of the treating physician. Ziltivekimab will not be available for prescription until marketing authorisation is issued.

Participants from some countries may have access to study intervention after end of the study. Argentina, Belgium, Brazil, France, Israel, Portugal, South Africa, Turkey, UK: see country/region-specific requirements (Appendix 11, Section 10.11).

6.7 Treatment of overdose

No overdose limit has been set, as a fatal outcome from unintentional overdose is considered to require a dose far beyond what can practically be administered using 1 mL prefilled syringes with a concentration of ziltivekimab 15 mg/mL. Based on the NOAEL in cynomolgus monkey and a 10-fold safety factor, the limit for a single ziltivekimab dose has been set at 250 mg. Based on the RESCUE-US study, phase 1 data and nonclinical data it is thus assessed that a single dose of ziltivekimab 50 mg or less in humans is not expected to lead to adverse events. For more information on overdose, also consult the current version of the ziltivekimab investigator's brochure[9] and any updates thereof.

There is no specific antidote for overdose with ziltivekimab. In the event of an overdose, the investigator should closely monitor the participant for overdose-related AEs/SAEs and laboratory abnormalities. In the event of overdose, appropriate supportive treatment should be initiated according to the participants' clinical signs and symptoms. Decisions regarding dose interruptions or modifications will be made by the investigator based on the clinical evaluation of the participant. A prolonged period of observation and treatment for these symptoms may be necessary, considering the long half-life of ziltivekimab.

Accidental overdose must be reported as a medication error. Intentional overdose must be reported as misuse and abuse, please refer to Section 8.3 and Appendix 3 (Section 10.3) for further details.

6.8 Concomitant therapy

6.8.1 Recording of concomitant therapy including therapies administered as part of standard of care

Concomitant therapy to be recorded in this study is concomitant medication. Any medication or vaccine (including over-the-counter or prescription medicines and COVID-19 vaccinations) that the participant is receiving at the time of randomisation or receives during the study must be recorded.

The information collected for each concomitant therapy includes:
- Trade name or generic name.
- Primary indication.
- Dose and unit, frequency, route of administration.
- Dates of administration including start and stop dates or continuation.
- Related AE number when applicable.

Special focus should be on recording standard of care including:
- HF medication
- Antihypertensive medication
- Diuretics
- ARNi
- GLP-1 RA

- SGLT-2i
- Atrial fibrillation/flutter medication including anticoagulants and antiarrhythmics

Adherence to standard of care will be assessed and documented at baseline. Participants with inadequate standard of care treatment, which in the investigator's opinion makes the participants' participation in the study inappropriate, are not eligible for enrolment (exclusion criterion #7). Furthermore, participants with unstable medical therapy (at the discretion of the investigator), including dose of diuretics, are not eligible for enrolment (exclusion criterion #8).

Changes to background therapy can take place during the study as part of standard of care for the participant or due to adverse events. If allowed according to local regulation, Novo Nordisk may compensate parts of the cost of some concomitant medication used to ensure adequate standard of care; see Section 6.4.3 and country/region-specific requirements (Appendix 11, Section 10.11).

Changes in concomitant therapy must be recorded at each visit. If a change is due to an AE, then this must be reported according to Section 8.3 and Appendix 3 (Section 10.3).

6.8.2 Restrictions to concomitant therapy

The following medications are not permitted during the study, in alignment with exclusion criteria #4 and #33, #35 and #36:

- Approved or non-approved investigational medicinal product.
- Live or attenuated-live vaccine products. If such vaccines are needed, study intervention should be paused for a minimum of 3 months before the live / attenuated-live vaccine is administered, and study intervention can be administered one month after the vaccination. Not-live and not attenuated-live vaccines are allowed during study conduct without pausing study intervention. For guidance refer to Appendix 9 (Section 10.9).
- Chronic use of systemic immunosuppressive drugs (both small molecules and biologics) or disease modifying anti-rheumatic drugs (DMARDs including both biologic DMARDs like anti-TNF-alpha and conventional DMARDs like methotrexate) *(Note: Use of otic, ophthalmic, inhaled, and topical corticosteroids or local corticosteroid injections are not exclusionary. Temporary systemic immunosuppressive treatment of e.g., chronic obstructive pulmonary disease [COPD] exacerbations is allowed)*.
- Use of anti-IL-6 products.

6.8.3 Coadministration of medication metabolised by CYP450

Cytochrome P450s in the liver are down regulated by infection and inflammation stimuli including cytokines such as IL-6. IL-6 modulators may restore CYP450 activities to normal levels leading to increased metabolism of drugs that are CYP450 substrates compared to metabolism prior to treatment with IL-6 modulators.

IL-6 concentrations in the study population are expected to correspond with IL-6 concentrations in healthy subjects.[52] Therefore, we do not expect the CYP450 activity to be downregulated in the study population. Hence, there is a low risk of a clinically relevant drug-drug interactions related to CYP450 enzymes because of a reduction in IL-6 concentration levels following treatment with ziltivekimab.

Upon initiation or discontinuation of ziltivekimab, in participants being treated with CYP450 substrates with a narrow therapeutic index, perform therapeutic monitoring of effect (e.g., warfarin), drug concentration (e.g., theophylline, phenytoin) or monitor participants closely until stable drug effects are achieved (e.g., pimozide, fentanyl) and adjust the individual medicinal product dose as needed. The effect of ziltivekimab on CYP450 enzyme activity may persist for several months after stopping therapy. Exercise caution when ziltivekimab is co-administered with CYP3A4 substrate drugs where a decrease in effectiveness would be undesirable e.g., hormonal contraceptives and CYP3A4 substrate statins. Modifying concomitant drugs to non-3A4 alternative drugs, e.g., rosuvastatin, pravastatin and fluvastatin, because of a drug-drug interaction concern, is at the discretion of the investigator. Formal drug-drug interaction studies with ziltivekimab have not been conducted.

7 Discontinuation of study intervention and participant discontinuation/withdrawal

Study participants will be followed for the complete duration of the study irrespective of their adherence to allocated study intervention or adherence to the protocol in general. Efforts must be made to keep the participants on study intervention and to have participants attend and complete all scheduled visit procedures. Study participants must be educated about the continued scientific importance of their data, even if they discontinue study intervention.

Discontinuation of specific sites or of the study as a whole is detailed in Appendix 1 (Section 10.1.11).

7.1 Discontinuation of study intervention

Study intervention (i.e., randomised treatment) may be discontinued at any time during the study at the discretion of the participant or at the discretion of the investigator for safety, behavioural, or compliance reasons.

Temporary discontinuation of study intervention is allowed at the discretion of the investigator. The primary reason for discontinuation of study intervention must be recorded in the eCRF. Date of last dose of study intervention should be recorded in the eCRF. Treatment discontinuation must be registered in RTSM/IWRS when a participant is on treatment pause and treatment resume must be registered in RTSM/IWRS when a patient resumes study intervention.

Study intervention should be resumed if the circumstances later allow. Similarly, participants who discontinue study intervention on their own initiative should be encouraged to resume the treatment.

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. In case of permanent discontinuation of study intervention, the primary reason for discontinuation of study intervention must be specified in eCRF, and final drug accountability must be performed. Treatment discontinuation must be registered in RTSM/IWRS.

Temporary or permanent discontinuation of study intervention will not lead to withdrawal from the study. Efforts must be made to have the participants who discontinue study intervention attend the planned visit schedule. As a minimum, participants who discontinue study intervention should come to the end of treatment visit (V-EoT), where the key assessments are to be made and as a minimum the primary endpoint and all confirmatory secondary endpoints, as well as important safety data, should be assessed. Details regarding participant withdrawal from the study are provided in Section 7.1.1 below.

7.1.1 Study intervention discontinuation criteria

Administration of study intervention (i.e., randomised treatment) may be discontinued temporarily or permanent during the study due to safety considerations.

Study participants meeting discontinuation criteria #1 to #3 are not allowed to resume study intervention if fulfilling the criteria.

Study participants meeting discontinuation criteria#4 to #16 should temporarily discontinue study intervention and study intervention can be resumed, if the criteria are no longer met. Confirmation of laboratory values and repeated testing may be performed at the local or central laboratory at the discretion of the investigator. Local laboratory test results must be documented in the participant's medical record.

Local requirements may apply. UK: see country/region-specific requirements (Appendix 11, Section 10.11).

The study intervention must be discontinued, if any of the following applies for the participant:
Conditions leading to permanent discontinuation of study intervention

1. Diagnosis of active tuberculosis, or active hepatitis C (positive anti-HCV and detectable HCV RNA) or hepatitis B (positive HBsAg and/or detectable HBV DNA).
2. Suspected severe systemic hypersensitivity to the product.
3. Gastrointestinal perforation or diverticulitis.

Conditions leading to temporary or permanent discontinuation of study intervention

4. Pregnancy.
5. Intention of becoming pregnant.
6. Latent tuberculosis.
7. Diagnosis of human immunodeficiency virus (HIV) and not receiving a stable antiretroviral regimen, at the discretion of the investigator.
8. Serious infections (infections leading to hospitalisation or use of i.v. antibiotics) or opportunistic infections.
9. Absolute neutrophil count $<1\times10^9$/L.
10. Platelet count $<100\times10^9$/L.
11. Abnormal liver blood parameters indicating drug induced liver injury (DILI[40]) in the form of:
    - ALT or AST >8xULN.
    - ALT or AST >5xULN and persists for more than 2 weeks.
    - ALT or AST >3xULN and (total bilirubin >2xULN or INR >1.5).
    - ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).
12. Administration of any of the disallowed medications (Section 6.8.2).
13. The participant is in need of receiving live or attenuated-live vaccinations.
14. Simultaneous use of an approved or non-approved investigational medicinal product in another clinical study.
15. Simultaneous use of an approved or non-approved device for the treatment of HF in another clinical study.
16. Other safety concerns, at the discretion of the investigator.

Ad 1: If HBV DNA is detected and quantifiable the participant should discontinue study intervention and be referred to a hepatology or infectious disease specialist. If HBV DNA is detected but not quantifiable a repeat test should be performed as soon as possible. If HBV DNA is also detected in the repeat test the participant should discontinue study intervention and be referred to a hepatology or infectious disease specialist. If HBV DNA is not detected on the repeat test the participant should continue study intervention and HBV DNA monitoring as planned.

Ad 2: In case of suspicion of a severe systemic hypersensitivity reaction[53] (i.e. not mild/moderate local reactions) to the investigational product, blood samples are recommended to be drawn as soon as possible and no later than 12 hours after the reaction; see Section 8.6.1 for details.

Ad 4 and 5: If a female participant intends to become pregnant, study intervention is recommended to be discontinued at least 5 half-lives (285 days, ~10 months) before the contraceptive method is stopped. If a female participant becomes pregnant unintentionally, study intervention must be discontinued immediately during pregnancy and breast feeding. The female participant will continue the other study procedures or will be followed-up via phone contacts.

Ad 6: Administration of study intervention can be resumed when TB treatment (according to local guidelines) has been initiated and the participant has undergone 28 days of treatment. If the participant discontinues TB treatment before the treatment regimen is completed as per the investigators discretion the participant must discontinue the study intervention.

Ad 7: Administration of study intervention can be resumed when the participant is on a stable antiretroviral regimen, at the discretion of the investigator.

Ad 8: Administration of study intervention can be resumed when all signs and symptoms of infection have been resolved. Opportunistic infections include[38]: but are not limited to: *Pneumocystis jirovecii*, BK virus disease including PVAN, Cytomegalovirus disease, Post-transplant lymphoproliferative disorder (EBV), Progressive multifocal leucoencephalopathy, Bartonellosis (disseminated disease only), Blastomycosis, Toxoplasmosis, Coccidioidomycosis, Histoplasmosis, Aspergillosis (invasive disease only), Candidiasis (invasive disease or pharyngeal), Cryptococcosis, Other invasive fungi: *Mucormycosis* (zygomycosis) (Rhizopus, Mucor and Lichtheimia), *Scedosporium/Pseudallescheria boydii, Fusarium*, Legionellosis, Listeria monocytogenes (invasive disease only), Nocardiosis, Non-tuberculous mycobacterium disease, Salmonellosis (invasive disease only), Herpes simplex (invasive disease only, not including herpes labialis or genital infections), Herpes zoster (any form), Strongyloides (hyperinfection syndrome and disseminated forms only), Paracoccidioides infections, *Penicillium marneffei, Sporothrix schenckii*, Cryptosporidium species (chronic disease only), Microsporidiosis, Leishmaniasis (Visceral only), Trypanosoma cruzi infection (Chagas' disease) (disseminated disease only), Campylobacteriosis (invasive disease only), Shigellosis (invasive disease only), Vibriosis (invasive disease due to *Vibrio vulnificus*).

Ad 9: Participants with a neutrophil count $<1\times10^9$/L should have repeat testing performed as soon as possible and should discontinue study intervention if confirmed. For participants with a confirmed neutrophil count of 0.5 to 1×10^9/L, study intervention can be resumed when the neutrophil count is $\geq1\times10^9$/L. Participants with a confirmed neutrophil count of $<0.5\times10^9$/L can only resume study intervention if an alternative aetiology has been identified and the neutrophil count is $\geq2\times10^9$/L.

Ad 10: Participants with a platelet count $<100\times10^9$/L should have repeat testing performed as soon as possible and should discontinue study intervention if confirmed. For participants with a confirmed platelet count of 50 to 100×10^9/L study intervention can be resumed when the platelet count is $\geq100\times10^9$/L. Participants with a confirmed platelet count of $<50\times10^9$/L can only resume

study intervention if an alternative aetiology has been identified and the platelet count is $\geq 120 \times 10^9$/L.

Ad 11: For all such events participants should temporarily discontinue study intervention and have repeat testing performed as soon as possible, and have potential alternative aetiologies identified. Participants where an alternative aetiology cannot be definitively identified or where liver blood parameters have not returned to pre-event levels must permanent discontinue study intervention and be monitored closely at the discretion of the investigator.

Ad 12: If disallowed medication is discontinued, administration of study intervention can be resumed if there are no safety concerns at the discretion of the investigator.

Ad 13: If such vaccines are needed, study intervention should be paused for a minimum of 3 months before the live / attenuated-live vaccine is administered (Appendix 9, Section 10.9), and study intervention can be administered one month after the vaccination.

Ad 14: Participants should be advised not to participate in other interventional clinical studies (i.e., registers and observational studies are permitted), while participating in this study. If done, administration of study intervention should be discontinued. If participation in the other study is stopped, administration of study intervention can be resumed if there are no safety concerns at the discretion of the investigator after discussing with a Novo Nordisk medical expert.

7.2 Participant discontinuation/withdrawal from the study

Study participants are expected to stay in the study for the entire study duration, irrespective of their adherence to allocated study intervention or adherence to the protocol in general. If study intervention is permanently discontinued, the participant should, if at all possible, remain in the study to be evaluated for key assessments; see Section 7.1 for details.

A participant may be withdrawn from the study at any time at the discretion of the investigator for safety, behavioural, or compliance reasons.

A participant may withdraw consent at any time at his/her own request.

If considering withdrawing from the study, the participant should, as an alternative, be offered flexible participation in the study. This could be attending fewer visits (i.e., reduced visit schedule), converting site visits to phone contacts, treatment pause, or only being followed-up for AEs, and outcomes related to the primary and first four secondary objectives. Another alternative could be to cease all study-related activities including study intervention, and simply receive a phone call at study end to collect AEs and CV outcomes. It must be explained to the participant that this must include information on their AEs and CV outcomes, especially those related to the primary objective that occurred since last contact to the participant. Only if the participant declines all alternatives, should the participant be recorded as withdrawn.

If a participant withdraws consent or is withdrawn by the investigator prior to randomisation, he/she will not be asked to have any follow-up assessment performed. The following data must be collected: Demography, available eligibility criteria, date of informed consent, date of screening

(day 1 of visit 1) and the date when participants participation ended. The end of study form must be completed.

If a participant withdraws consent or is withdrawn by the investigator after randomisation, the investigator must ask the participant if he/she is willing, as soon as possible, to have assessments performed according to the EoT visit. See flowchart (Section 1.2) for data to be collected.

If the participant withdraws consent, Novo Nordisk may retain and continue to use any data collected before such a withdrawal of consent for the purpose of the study or scientific research. If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the medical record and notify the sponsor as soon as possible.

Final study intervention accountability must be performed even if the participant is not able to come to the site. Discontinuation of treatment must be registered in the RTSM/IWRS.

Although a participant is not obliged to give his/her reason(s) for withdrawing, the investigator must make a reasonable effort to ascertain the reason(s), while fully respecting the participants' rights. Where the reasons are obtained, the primary reason for withdrawal must be specified in the eCRF.

For participants who are withdrawn, when the study comes to an end, the investigator must scrutinise publicly available registries to determine vital status, unless prohibited by local regulations or specifically prohibited by the participant upon withdrawal of consent. Please also refer to Section 4.4.1 for further details.

Local requirements may apply. Mexico: see country/region-specific requirements (Appendix 11, Section 10.11).

7.2.1 Replacement of participants

If a participant discontinues study intervention, withdraws consent or is withdrawn by the investigator, he/she will not be replaced.

7.3 Lost to follow-up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. A participant cannot be declared lost to follow-up before all the attempts have been repeated and the study has come to an end as described in Section 4.4.1.

The following actions must be taken if a participant fails to return to the site for a required visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, at least three telephone calls and, if necessary, a certified letter to the participants' last known mailing address or local equivalent methods, as described in Section 4.4.1). These contact attempts should be documented in the

participant's source document. Contact attempts will be made in accordance with local legislation.

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of `lost to follow-up'.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomised, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Local requirements may apply. France; see country/region-specific requirements (Appendix 11, Section 10.11).

8 Study assessments and procedures

The following sections describe the assessments and procedures, while their timing is summarised in the flowchart, Section 1.2.

The following general assessments and procedures must be followed in the study:

Activities related to study enrolment

- Informed consent must be obtained before any study-related activity (Appendix 1, Section 10.1.3). Consent for optional collection of samples for future research (genetic analysis and circulating biomarkers; see Sections 8.7 and 8.8) will also be obtained. Furthermore, consent for optional use of the CardioSignal app (selected countries only) will be obtained (Section 8.12.3).
- Prior to randomisation of the patient at visit 2, all screening evaluations must be completed and reviewed to confirm that potential participants meet all inclusion criteria and none of the exclusion criteria.
- The investigator will maintain a screening log to record details of all participants screened and rescreened, and to confirm eligibility or record reason for screen failure, as applicable.
- At screening, participants will be provided with a card stating that they are participating in a study and giving contact details of relevant study site staff that can be contacted in case of emergency.
- The investigator should inform the participants primary physician about the participant's participation in the study if the participant has a primary physician and if the participant agrees to the primary physician being informed.
- Each participant should be asked to provide contact information for persons (preferably at least 3), e.g., relatives, primary care provider or other, whom investigator can contact in case of issues when trying to contact the participant during the study. The sites are encouraged to maintain these details as current as possible throughout the course of the study.

Activities related to scheduled visits and contacts

- Adherence to the study design requirements, including those specified in the flowchart (Section 1.2), is essential and required for study conduct.
- The investigator must ensure they keep regular contact with each participant throughout the entire study, and at all times have updated contact information.
- It is the responsibility of the investigator to schedule visits including laboratory assessments and contacts as per protocol (see flowchart, Section 1.2) and to ensure they take place. For study intervention compliance see Section 6.4.2.
- In cases of missed visits, the site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study. Even if a visit (or phone contact) is missed and it is not possible to re-schedule, the investigator must take every effort to have all participants followed for endpoint-related outcomes including CV-death and HF hospitalisation or urgent HF visits.
- Participants should download the study app to their own smartphones and receive training in its use by the investigator or delegated site staff before entering any study-related data. Participants who do not have a suitable smartphone will be provided with a device on which the study app

has been preloaded. Additionally, a tablet with the study app will be available at the sites for back-up in cases where the participant has pending tasks to complete in the app.
The study app will contain screens related to the following:

- Recording of the date, time and site of injection (abdomen, thigh, or upper arm) of each dose administered (Section 6.1.2).
- KCCQ questionnaire including PGI-S for KCCQ and PGI-C for KCCQ (Section 8.1.2.1).
- EQ-5D-5L questionnaire (Section 8.11.1).
- Optional patient engagement tools (Section 8.12).
- Reminders etc.

In addition, the study app will contain a section ('Patient Connect') with relevant materials:

- Instruction video of a patient taking the study intervention (Section 6.1.2).
- Study introduction video
- FAQ
- Newsletters

Local requirements may apply: Portugal: see country/region-specific requirements (Appendix 11, Section 10.11).

- If necessary, in order to retain the participant in the study, sites visits can be replaced by phone contact. However, as a minimum, participants should be asked to attend the key visits: V1, V2, V3, V5, V6, V7, V8 and visits every 6 months (V10, V12, V14, V16, V18), end of treatment visit (V-EoT) and end of study visit (V-EoS) as face-to-face visits as these are key assessment visits. If a site visit is changed to a phone contact the investigator needs to ensure that the participant has enough study intervention within the expiry date.
- In case local restrictions leading to lockdown of a site or pharmacy or a restriction of movement of participants, site visits can be performed as home nursing (Appendix 10, Section 10.10).

Details on study procedures and assessments

- There are no fasting visits.
- Assessments should be carried out according to the clinic's standard of practice unless otherwise specified in the current section. Efforts should be made to limit the bias between assessments (i.e., performing participant-recorded assessments before other assessments, measuring vital signs before blood draws).
- All assessments and procedures at a given study visit do not need to be performed on the same day, provided that they are completed within the visit window. Refer to Section 8.2.3.2 for visit window details related to echocardiography.
- At the randomisation visit (visit 2), all baseline procedures and assessments must be performed prior to dosing.
- Blood samples should be drawn prior to dosing at visits 2, 3 and 5.
- Repeat samples may be taken for technical issues and unscheduled samples or assessments may be taken for safety reasons. Local CRP/hs-CRP testing should only be performed if deemed clinically necessary by the investigator due to the risk of unblinding. Please refer to Appendix 2 (Section 10.2) for further details on laboratory samples.
- The ePRO questionnaires, including the KCCQ, PGI and EQ-5D-5L, should be completed prior to assessments and blood sampling within the visit window specified in the flowchart (Section 1.2).

- Review of ePRO questionnaires, including the KCCQ, PGI and EQ-5D-5L, ECGs, echocardiographic reports, laboratory reports, etc. must be documented in the source documents or in the participant's medical record. The review must be performed by an investigator. In case of detection of AEs, this should be reported as applicable. If clarification of entries or discrepancies in the ePRO questionnaires is needed, the participant must be questioned, and a conclusion made in the participant's source documents. Care must be taken not to bias the participant.
- Deaths, HF hospitalisation and urgent HF visit, and infections of special interest will be evaluated by a blinded event adjudication committee (EAC) on an ongoing basis (Section 8.3, Table 8-1 and Appendix 8, Section 10.8).
- An external data monitoring committee will review and evaluate accumulated unblinded data from the study at predefined time points as well as *ad hoc* (Section 10.1.6.2).
- Future biomarker testing is planned and will not be included in the clinical study report (CSR) (Sections 8.7 and 8.8).

8.1 Efficacy assessments

Efficacy of ziltivekimab will be assessed based on morbidity/mortality, health status and laboratory biomarkers, reflecting the study endpoints (Section 3). Furthermore, effects of ziltivekimab on atrial fibrillation will be based on adverse events requiring additional data collection (Section 8.3).

Planned time points for all efficacy assessments are provided in the flowchart (Section 1.2).

8.1.1 Clinical efficacy laboratory assessments

Biomarkers of efficacy include biomarker of inflammation (hs-CRP), biomarker of HF/myocardial strain (NT-proBNP) and biomarker of kidney function (eGFR).

All protocol-required laboratory assessments and laboratory components of composite endpoints, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the flowchart (Section 1.2) and the laboratory manual.

eGFR will be calculated by the central laboratory based on the creatinine value using the CKD-EPI equation.[10] For the central laboratory calculation of the eGFR information on year of birth will be collected on the laboratory requisition form (Appendix 2, Section 10.2, Table 10-1). For calculation of eGFR, 01-July of the year of birth will be used.

Local requirements may apply. China: see country/region-specific requirements (Appendix 11, Section 10.11).

8.1.2 Health status

8.1.2.1 Kansas City Cardiomyopathy Questionnaire

The health status will be assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ) version 2.0.[54] KCCQ measures Health-Related Quality of Life (HRQOL) and is a disease-specific health status instrument for HF. The approximate completion time is 4-6 minutes.

The questionnaire consists of 23 items yielding:

- 7 domain scores (score range):
    - Physical limitation (0-100)
    - Symptom frequency (0-100)
    - Symptom severity (0-100)
    - Symptom stability (0-100)
    - Self-efficacy and knowledge (0-100)
    - Quality of life (0-100)
    - Social limitation (0-100)
- 2 summary scores (score range):
    - Total symptom score (0-100)
    - Clinical summary score (CSS) (0-100)
- Overall summary score (score range: 0-100)

Scores range from 0 to 100, with 0 as the lowest score and 100 as the highest score. Higher scores indicate better health status, fewer symptoms, and greater disease-specific health related quality of life, respectively. The overall summary score and all domains have been independently demonstrated to be valid, reliable, and responsive to clinical change.[54]

The Patient Global Impression of Severity (PGI-S) and Patient Global Impression of Change (PGI-C) scales will be used to help interpret the clinical meaningfulness of change in KCCQ summary score. Both scales are a global index and are simple, direct, easy to use scale that is intuitively understandable to clinicians. The following ePRO questionnaires will be used:

- Patient Global Impression of Severity (PGI-S) for KCCQ version 1.0.
- Patient Global Impression of Change (PGI-C) for KCCQ version 1.0.

Participants should be given the opportunity to complete the questionnaires by themselves without interruption. The questionnaires should be completed in close relation to the visits, prior to or at the visit. Planned time points for the KCCQ and associated PGI scores are provided in the flowchart (Section 1.2). Participants should complete the questionnaire using the study app. Participants are not allowed to answer the questions on paper.

Completed KCCQ and PGI questionnaires must be reviewed by the investigator, and the review must be documented in the medical records. If clarification of entries or discrepancies in the questionnaires is needed, the participant must be questioned, and a conclusion made in the participant's source documents. Care must be taken not to bias the participant. In case of detection of AEs, this should be reported as applicable (Section 8.3 and Appendix 3, Section 10.3).

8.1.3 Physical limitations

8.1.3.1 NYHA score

The New York Heart Association (NYHA) classification provides a simple way of classifying the extent of HF. It classifies patients in one of four categories based on their limitations during physical activity; the limitations/symptoms are in regard to normal breathing and varying degrees in shortness of breath and or angina pain.

NYHA Classification - The stages of HF:

- Class I: No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea.
- Class II: Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea
- Class III :Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnoea
- Class IV: Unable to carry on any physical activity without discomfort. Symptoms of HF at rest. If any physical activity is undertaken, discomfort increases.
- No NYHA class listed or unable to determine.

The NYHA score is to be assessed at screening, baseline and during the study; see flowchart (Section 1.2) for details.

8.1.4 Morbidity and mortality

8.1.4.1 Hospitalisations

SAE hospitalisations

Hospitalisations which are related to a SAE (Appendix 3, Section 10.3), including re-admissions for the same event, should be reported on the AE form and safety information form (SIF). Admission and discharge dates will be recorded on the SIF.

Furthermore, selected hospitalisations and urgent visits will be evaluated by the EAC (Table 8-1 and Section 8.1.4.1):

- HF hospitalisation or urgent HF visit.
- Hospitalisation with infection as primary cause.

Non-SAE hospitalisations

Hospitalisations that are not related to SAEs should be reported on the 'Non-SAE hospitalisations' form. This includes the below types of hospitalisations:

- Hospitalisation for elective treatment of a pre-existing condition that did not worsen from randomisation.
- Hospitalisations for administrative, study-related and social purposes.
- Hospital admissions for surgical procedures, planned before randomisation.

8.1.4.2 Events confirmed by Event Adjudication Committee

Deaths, HF hospitalisations and urgent HF visits will be evaluated by the event adjudication committee (EAC) on an ongoing basis (see Section 8.3, Table 8-1 and Appendix 8, Section 10.8 for details).

8.2 Safety assessments

The safety profile of ziltivekimab will be based on assessments of EAC-confirmed events, and monitoring of safety based on physical examination, vital signs, clinical laboratory safety

assessments, concomitant illness and reporting of adverse events. Details on reporting of adverse events including EAC evaluation of events are provided in Section 8.3.

Planned time points for all safety assessments are provided in the flowchart (Section 1.2).

8.2.1 Physical examinations

Physical examinations should be performed by the investigator at baseline (randomisation at visit 2), at yearly (visits 8, 12 and 16) and at end of treatment (V-EoT) (see flowchart in Section 1.2).

The physical examination should be performed according to local procedures and will, as a minimum, include assessments of the:

- Signs of HF.
- Cardiovascular system.
- Respiratory system.
- Gastrointestinal system including mouth and abdomen.
- Extremities.
- Skin (full body examination with focus on wounds and infections).
- General appearance.

The investigators should pay special attention to clinical signs related to previous serious illnesses. Relevant findings in the physical examination present at or prior to randomisation should be recorded on the Medical History/Concomitant Illness form in the eCRF in accordance with Section 8.2.5. Findings not present at randomisation should be reported as AEs according to Section 8.3.2.

Body measurements (e.g., height, waist circumference and weight) will also be measured and recorded as specified in the flowchart (Section 1.2). Height should be assessed without shoes. For body weight measurements, the participant is allowed to wear indoor, daytime clothing with no shoes. Waist circumference is defined as the abdominal circumference located midway between the lower rib margin and the iliac crest. Measurement must be obtained in standing position with a non-stretchable measuring tape and to the nearest cm or inch. The tape should touch the skin but not compress soft tissue and twists in the tape should be avoided. The participant should be asked to breathe normally.

8.2.2 Vital signs

Pulse rate as well as systolic and diastolic blood pressure should be assessed in accordance with the flowchart (Section 1.2).

Blood pressure and pulse rate measurements should be assessed in a sitting position with a completely automated device. Manual techniques should be used only if an automated device is not available. Blood pressure and pulse rate measurements should be preceded by at least 5 minutes of rest for the participant in a sitting position and a quiet setting without distractions (e.g., no use of television, cell phones). Study participants with uncontrolled hypertension (defined as an average systolic blood pressure ≥180 mmHg) at screening are not eligible for inclusion in the study (see exclusion criterion #14).

Blood pressure will consist of 3 systolic and diastolic blood pressure measurements with intervals of at least 1-2 minutes. An additional fourth blood pressure measurement must be performed if the first two readings on systolic or diastolic blood pressure differ by >10 mmHg. No more than four measurements should be performed.

- The mean systolic and diastolic blood pressure values are calculated based on the last 2 measurements.
- The last 2 systolic and last 2 diastolic blood pressure measurements should be recorded in the eCRF. The eCRF will calculate the mean of the last 2 measurements.

Pulse rate will be measured in connection to the blood pressure measurements.

- The mean pulse rate value is calculated based on the last 2 pulse rate measurements.
- The pulse rate for the last 2 measurements should be recorded in the eCRF. The eCRF will calculate the mean of the last 2 measurements.

The exact measured values should be recorded without rounding in the eCRF.

8.2.3 Electrocardiograms and echocardiography

8.2.3.1 Electrocardiograms

A 12-lead ECG will be obtained as outlined in the flowchart (Section 1.2) using an ECG machine that automatically calculates the heart rate.

The ECG must be interpreted (categorised as normal or abnormal, and, if abnormal, furthermore indicate whether the finding was clinically relevant), signed and dated by the investigator and filed on the participant's medical record (Appendix 1, Section 10.1.9). The ECG measures and corresponding outcomes should be recorded in the eCRF. Furthermore, the investigator is to assess presence of ongoing atrial fibrillation or flutter.

Patients with a heart rate above 110 or below 40 beats per minute as evaluated on the ECG performed at screening (visit 1) are not eligible for inclusion in the study (see exclusion criterion #15).

Any abnormal clinically relevant findings revealing baseline conditions are to be reported as concomitant illness/medical history in the eCRF (Section 8.2.5). Any clinically relevant worsening of a pre-existing condition as well as any new clinically relevant signs, symptoms or disease found as a result of the ECGs conducted after randomisation are to be reported as AEs (Section 8.3 and Appendix 3, Section 10.3).

Additional ECG recordings can be performed at the investigator's discretion, in which case the reason is to be documented, and an AE reported if applicable.

8.2.3.2 Echocardiography

A standard echocardiographic examination must be performed at screening (visit 1) in order to assess inclusion criteria #6 (LVEF) and #7 (structural heart disease *and/or* functional heart disease), if a representative echocardiography has not been done within 12 months prior screening. Echocardiographic imaging should be performed locally by personnel trained in echocardiography.

8.2.4 Clinical safety laboratory assessments

All protocol-required safety laboratory assessments, including laboratory assessments of haematology, biochemistry, lipids, serology, tuberculosis, pregnancy and testing in case of systemic hypersensitivity (as defined in Appendix 2; Section 10.2, Table 10-2), must be conducted in accordance with the flowchart (Section 1.2) and the laboratory manual. Note that some biochemistry/haematology assessments are performed less frequently (biochemistry/haematology: ferritin, haptoglobin, transferrin, transferrin saturation, haematocrit, MCH, MCHC, MCV, reticulocyte count at V2, V5 and V8 only).

The investigator must review all laboratory results. Any abnormal clinically relevant findings revealing baseline conditions are to be reported as concomitant illness/medical history (Section 8.2.5). Study participants with abnormal laboratory values of specific concern, may fulfil exclusion criteria based on laboratory values (criteria #9 to #12 and #27), and should not be enrolled in the study.

Any clinically relevant worsening of a pre-existing condition as well as any new clinically relevant signs, symptoms or disease found as a result of the laboratory safety assessments conducted after randomisation are to be reported as AEs (Section 8.3). Study participants with abnormal laboratory values of specific concern, may fulfil discontinuation criteria (criteria #1, #4, #9 to #11) and study intervention should be discontinued temporary or permanent as specified in Section 7.1.1.

Local requirements may apply. China: see country/region-specific requirements (Appendix 11, Section 10.11).

8.2.5 Medical history and concomitant illness

Medical history is a medical event that the participant experienced prior to the time point from which AEs are collected, i.e., prior to initial dose of study intervention.

A **concomitant illness** is any illness that is already present at the time point from which AEs are collected or found as a result of a screening procedure or other study procedures performed before exposure to study intervention under clinical investigation.

In case of an abnormal and clinically relevant finding fulfilling the definition of medical history or concomitant illness, the investigator must record the finding on the medical history/concomitant illness form if it is present before initial dose of study intervention. Any new finding or worsening fulfilling the AE definition during the study from initial dose of study intervention must be reported (Section 8.3 and Appendix 3, Section 10.3).

All relevant concomitant illness/medical history, including COVID-19, must be recorded in Medical History/Concomitant Illness forms with special attention to:

- History of heart failure. This also includes each medical condition(s) that qualified the participants for participation in the study according to inclusion criteria #4 to #7.
- History of cardiovascular diseases.
- History of chronic kidney disease.

- History of infections (serious infections [infections leading to hospitalisation or use of i.v. antibiotics, i.v. antiviral or i.v. antifungal treatment], recurrent infections or opportunistic infections).
- History of malignant neoplasms.
- History of diabetes.
- History of liver disease (*Note: Child-Pugh score should be collected in a separate form in participants with a history of liver disease, see below*).

Child-Pugh Score

The Child-Pugh Score will be used to grade the degree of hepatic impairment in participants with a medical history of liver disease at randomisation. Assessment of encephalopathy and ascites should be based on medical history and the continued presence of encephalopathy and ascites at randomisation should be assessed at the investigator's discretion. Levels of bilirubin, albumin, and international normalized ratio (INR) should be based on historical local measurements. For all laboratory measurements the most recent results that are reflective of the participants habitual hepatic function should be used and results that are up to 12 months old are acceptable. The individual components of the Child-Pugh Score should be recorded in the eCRF.

8.2.6 Infections

Infections have been identified as a potential risk for ziltivekimab due the effect on neutrophils. Vigilance for timely detection of infections that may progress in severity is recommended, as signs and symptoms of acute inflammation may be lessened because of suppression of the acute-phase reaction.

Participants will be monitored closely throughout the study for infections. Study participants must be instructed to contact their physician immediately when any symptoms suggesting infection appear, to ensure rapid evaluation and appropriate treatment. For further details kindly refer to the document including information and cautions to be taken when handling infections during ziltivekimab administration.

Event adjudication committee evaluation of infections

Infections of special interest will be evaluated by the EAC on an ongoing basis (see Section 8.3 and Appendix 8, Section 10.8 for details).

8.2.7 Tuberculosis screening

Screening for tuberculosis (TB) must be performed before randomisation applying a multi-tiered approach:

- Step 1: Screen for risk factors for latent TB. If no risk factors are identified the participant is eligible for randomisation. A general guidance of TB risk factors is provided in a separate document.
- Step 2: If one or more TB risk factors are identified, the participant must undergo testing for latent TB with a central lab QuantiFERON-TB test unless the participant has a QuantiFERON-TB or T-SPOT.TB test no more than 90 days old at screening (visit 1), documented in medical records.

The standard results for TB test from the central laboratory are:

- Positive.
- Negative.
- Indeterminate.

In case of an indeterminate test, the test should be repeated. If the TB test result is 'Indeterminate' a retest should be performed as soon as possible. If the test is negative the participant is eligible for randomisation.

Study participants with history or evidence of latent TB are eligible if treatment of TB has been initiated at least 28 days before randomisation, in accordance with exclusion criterion #26.

If the participant has history or evidence of untreated latent TB at screening and treatment for latent TB is initiated during the screening period, the period can be extended from 5 weeks to a maximum of 8 weeks. This to allow for at least 28 days of treatment before randomisation without the need for re-screening the participant.

If the participant discontinues TB treatment before the treatment regimen is completed as per the investigators discretion the participant must not be randomised or must discontinue the study intervention if randomised.

Local requirements may apply. Argentina, Czech Republic, Germany, Latvia, Lithuania: see country/region-specific requirements (Appendix 11, Section 10.11).

8.2.8 Hepatitis B virus DNA monitoring

HBV DNA should be assessed in patients with positive anti-HBc at screening (visit 1).

The standard results for HBV DNA from the central laboratory are:

- Detected, quantifiable
- Detected, not quantifiable
- Not detected.

If HBV DNA is detected but not quantifiable a repeat test should be performed as soon as possible. If HBV DNA is also detected in the repeat test the participant is not eligible for enrolment and should be referred to a hepatology or infectious disease specialist. If HBV DNA is not detected on the repeat test the participant is eligible for enrolment.

Participants who are anti-HBc positive and HBV DNA negative (not detected) at screening (V1) are eligible for enrolment in the study but must be monitored with HBV DNA as indicated in the flowchart (Section 1.2).

Please refer to Section 7.1.1 for actions to be taken in response to results from HBV DNA monitoring during the study.

8.2.9 Pregnancy testing

A pregnancy test must be performed in women of childbearing potential (WOCBP) at each visit, i.e., at screening, at baseline, during the treatment period and at the follow-up visit (see flowchart in Section 1.2).

- WOCBP should only be included after a negative highly sensitive urine pregnancy test (refer to Appendix 2, Section 10.2).
- Home urine pregnancy testing may be performed between visits during the study, if additional urine pregnancy testing is required locally.
- Pregnancy testing should be performed whenever a menstruation is missed or when pregnancy is otherwise suspected.
- A pregnancy test should be performed at the end of relevant systemic exposure (at follow-up visit or at next site visit in case of premature discontinuation of study intervention).
- If the study visit is a phone contact, the participant can take the urine test at home and inform the investigator of the result. Home pregnancy kits will be provided.
- Additional pregnancy testing should be performed during the treatment period, if required locally; see country/region-specific requirements (Appendix 11, Section 10.11).

Local urine testing using a highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test is standard (Appendix 2, Section 10.2 and Table 10-2). Highly sensitive serum testing (sensitivity of 5-25 mIU/mL) is mandatory if required by local regulations or ethics committees, or to resolve an indeterminate test or to confirm a positive urine test.

Local requirements may apply. Argentina, Austria, Czech Republic, Germany, Italy, Poland, Portugal, Romania, South Korea, UK: see country/region-specific requirements (Appendix 11, Section 10.11).

8.3 Adverse events and other safety reporting

The investigator is responsible for detecting, documenting, recording and following up on events that meet the definition of an AE or SAE. The definition of AEs and SAEs can be found in Appendix 3 (Section 10.3).

Suspected COVID-19 should be reported if the clinical presentation is suggestive of COVID-19, even in the absence of a COVID-19 test or without a positive COVID-19 test result. In the absence of clinical symptoms, a positive COVID-19 test (antigen or antibody) should be reported.

Some AEs require additional data collection on a specific event form. The relevant events are listed below in Table 8-1, together with events for adjudication. The events listed in Table 8-1 must always be reported on an AE form and a specific event form and/or adjudication form must be completed. Reporting timelines can be found in Appendix 3 (Section 10.3).

For each event relevant for adjudication, an event type specific adjudication form should be completed in the CRF within 7 days (Figure 10-1). Event adjudication will be performed in randomised participants and will be evaluated by an independent external event adjudication committee (EAC) in a blinded manner (Appendix 1, Section 10.1.6.4 and Appendix 8, Section 10.8). Descriptions of the events mentioned in Table 8-1 is to guide investigators with regards to reporting of AEs.

Table 8-1 AEs requiring additional data collection and events for adjudication

Event type (AE category) including description	AE requiring additional data collection	Event for adjudication
Deaths and cardiovascular events		
Death All-cause death including CV-death, death due to infection, other known cause of death (non-CV, not due to infection) and unknown cause of death		X
Heart failure hospitalisation and urgent heart failure visit[a] New episode or worsening of existing heart failure leading to an urgent, unscheduled hospital admission or clinic/office/emergency department visit.		X
Acute myocardial infarction (AMI) Conditions include all types of acute myocardial infarction.	X	
Stroke Episode of focal or global neurological dysfunction that could be caused by brain, spinal cord, or retinal vascular injury as a result of haemorrhage or ischaemia, with or without infarction	X	
Atrial fibrillation Supraventricular tachyarrhythmia with uncoordinated atrial electrical activation	X	
Kidney events		
Events leading to kidney replacement therapy Initiation of dialysis treatment (haemodialysis or peritoneal dialysis) or kidney transplantation *Note: The underlying condition should be reported as the AE diagnosis*	X	
Acute kidney injury Abrupt decrease in kidney function, e.g., one of the following: • ≥ 0.3 mg/dL (≥ 26.5 µmol/L) increase in serum creatinine within 48 hours • ≥ 1.5 times increase in serum creatinine within 7 days • urine volume < 0.5 mL/kg/h for 6 hours	X	
Infections		
Infections of special interest • All SAEs caused by infections • All AEs (irrespective of seriousness) of: o Diverticulitis o Opportunistic infections[b]		X
Other type of events		
Neoplasms (malignant and non-malignant) All neoplasms (both malignant and non-malignant) confirmed by histopathology or other substantial clinical evidence	X	
Thrombocytopenia Thrombocytopenia is sustained platelet count < 100 x 10^9L). Signs of bleeding can also be the first sign of thrombocytopenia.	X	

Event type (AE category) including description	AE requiring additional data collection	Event for adjudication
Hepatic event Abnormal liver blood parameters indicating drug induced liver injury (DILI[40]) in the form of: • ALT or AST >8xULN. • ALT or AST >5xULN and persists for more than 2 weeks. • ALT or AST >3xULN and (total bilirubin >2xULN or INR >1.5). • ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).	X	
Hypersensitivity Hypersensitivity is defined as episodes of objectively reproducible symptoms or signs initiated by exposure to a defined stimulus at a dose tolerated by normal persons. Hypersensitivity includes: • local reactions, excluding injection site reactions • systemic reactions, including anaphylaxis. Anaphylaxis is defined as serious hypersensitivity reactions that is rapid in onset and may cause death.	X	
Injection site reaction Injection site reaction is inflammation in or damage to the tissue surrounding where a drug was injected.	X	

Medication error, misuse and abuse
Medication error:
• A medication error is an unintended failure in the IMP treatment process that leads to, or has the potential to lead to, harm to the participant, such as:
  • administration of wrong drug. *Note: Use of wrong DUN is not considered a medication error unless it results in administration of wrong drug.*
  • wrong route of administration, such as intramuscular instead of subcutaneous.
  • accidental administration of a lower or higher dose than intended. The administered dose must deviate from the intended dose to an extent where clinical consequences for the study participant were likely to happen as judged by the investigator, although they did not necessarily occur.
  • Treatment pauses/drug holidays should not be reported as a medication error.
 	
Misuse and abuse:
  • Situations where the IMP is intentionally and inappropriately used not in accordance with the protocol (e.g., overdose to maximise effect)
  • Persistent or sporadic, intentional excessive use of an IMP which is accompanied by harmful physical or psychological effects (e.g., overdose with the intention to cause harm)
Note: Medication error, misuse and abuse must always be reported on an AE form and the specific event form must be completed. The AE diagnosis on the AE form must reflect what occurred (e.g., accidental overdose, intentional overdose or other). If the medication error and/or misuse and abuse resulted in a clinical consequence, this must be reported on an additional AE form.
	X	

Notes:

[a] An urgent heart failure visit is defined as an event that meets the below 2 criteria:

1) The patient has an urgent, unscheduled office/practice or emergency department visit for a primary diagnosis of HF, but not meeting the criteria for a HF hospitalisation,

2) The patient receives at least ONE of the following treatments specifically for HF:
   a) Initiation of intravenous diuretic or vasoactive agent (e.g., inotrope, vasopressor, or vasodilator) (Note that significant augmentation of oral diuretic therapy will NOT be sufficient to fulfil the urgent HF visit criteria).
   b) Mechanical or surgical intervention, including:
      i) Mechanical circulatory support (e.g., intra-aortic balloon pump, ventricular assist device, extracorporeal membrane oxygenation, total artificial heart)
      ii) Mechanical fluid removal (e.g., ultrafiltration, haemofiltration, dialysis)

[b] Opportunistic infections include but are not limited to: *Pneumocystis jirovecii*, BK virus disease including PVAN, Cytomegalovirus disease, Post-transplant lymphoproliferative disorder (EBV), Progressive multifocal leucoencephalopathy, Bartonellosis (disseminated disease only), Blastomycosis, Toxoplasmosis, Coccidioidomycosis, Histoplasmosis, Aspergillosis (invasive disease only), Candidiasis (invasive disease or pharyngeal), Cryptococcosis, Other invasive fungi: *Mucormycosis* (zygomycosis) (Rhizopus, Mucor and Lichtheimia), *Scedosporium/ Pseudallescheria boydii, Fusarium*, Legionellosis, Listeria monocytogenes (invasive disease only), Tuberculosis, Nocardiosis, Non-tuberculous mycobacterium disease, Salmonellosis (invasive disease only), HBV reactivation, Herpes simplex (invasive disease only, not including herpes labialis or genital infections), Herpes zoster (any form), Strongyloides (hyperinfection syndrome and disseminated forms only), Paracoccidioides infections, *Penicillium marneffei, Sporothrix schenckii*, Cryptosporidium species (chronic disease only), Microsporidiosis, Leishmaniasis (Visceral only), Trypanosoma cruzi infection (Chagas' disease) (disseminated disease only), Campylobacteriosis (invasive disease only), Shigellosis (invasive disease only), Vibriosis (invasive disease due to *Vibrio vulnificus*) and HCV progression.[38]

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CV = cardiovascular; DUN = dispensing unit number; EBV = Epstein-Barr virus; HBV = hepatitis B virus; HCV = hepatitis C virus; IMP = investigational medicinal product; PVAN = polyomavirus-associated nephropathy; SAE = serious adverse event; ULN = upper limit of normal reference range.

8.3.1 Time period and frequency for collecting adverse event information

All AEs and SAEs must be collected from first administration of study intervention (at randomisation visit, i.e., visit 2) and until the end of study visit (V-EoS), in accordance with the flowchart (Section 1.2) or whenever, within the above time period, the site becomes aware of an AE or SAE.

Conditions present prior to the timepoint from which AEs are collected and anticipated day-to-day fluctuations of these conditions, including those identified during screening or during other study-related procedures performed before exposure to study intervention under clinical investigation, will be recorded as medical history/concomitant illness.

AE and SAE reporting timelines can be found in Appendix 3 (Section 10.3). All SAEs must be recorded and reported to Novo Nordisk or designee without undue delay but not later than within 24 hours of obtaining knowledge of the events. Similarly, the investigator must submit any updated SAE data to Novo Nordisk or designee without undue delay but not later than within 24 hours of obtaining knowledge of the information.

Investigators are not obligated to actively seek for AE or SAE in former study participants. However, if the investigator learns of any SAE with a suspected causal relationship to study intervention, or to study participation, occurring after a participant has discontinued/completed the study, the investigator must notify Novo Nordisk without undue delay.

8.3.2 Method of detecting adverse events

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

Care should be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about events.

8.3.3 Follow-up of adverse events

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs should be followed until final outcome of the event or until the participant is lost to follow-up as described in Section 7.3. Further information on follow-up and final outcome of events is given in Appendix 3 (Section 10.3).

8.3.4 Regulatory reporting requirements for serious adverse events

Prompt notification by the investigator to Novo Nordisk of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

Novo Nordisk has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. Novo Nordisk will comply with country/region-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators. This also includes suspected unexpected serious adverse reactions (SUSARs).

An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from Novo Nordisk will review and then file it along with the investigator's brochure[9] and will notify the IRB/IEC, if appropriate according to local requirements.

To avoid introducing bias and to maintain the integrity of the primary analysis, Novo Nordisk will exempt SAEs that are part of the primary objective evaluation (i.e., components of the primary endpoint; see Section 3) from unblinding during regulatory reporting, even though the cases fulfil the definition of SUSARs. The independent data monitoring committee (DMC) (Appendix 1, Section 10.1.6.2) receives unblinded data and makes recommendations to the Novo Nordisk safety committee (Appendix 1, Section 10.1.6.1) on an ongoing basis. This ensures adequate monitoring of safety while maintaining SAE reports related to the primary endpoint blinded for Novo Nordisk.

At the end of the study, when treatment is revealed, all exempted cases which meet the criteria for expedited reporting SUSARs will be submitted to the regulatory authorities. Because multiple cases will be identified simultaneously, Novo Nordisk will not be able to fulfil the 7 days requirement for fatal or life-threatening events but will within 60 days after code break have all SUSARs submitted to the regulatory authorities.

In case a regulatory authority requires the blinded report on an expedited basis, Novo Nordisk will submit individual blinded case reports related to IMP to the relevant regulatory authorities on an expedited basis.

8.3.5 Pregnancy

It must be recorded at screening (visit 1) whether female participants are of childbearing potential (see Appendix 4, Section 10.4.1 for details).

Details of pregnancies in female participants will be collected after first exposure to study intervention and until follow-up (V-EoS). If a female participant becomes pregnant, the investigator should inform Novo Nordisk within 14 calendar days of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4.3).

8.3.6 Cardiovascular and death events

All-cause mortality and prespecified cardiovascular events will be assessed as events with additional data collected or will undergo independent blinded evaluation by the EAC as specified in Table 8-1 and described in Appendix 8, Section 10.8.

8.3.7 Adverse events of special interest

No adverse events have been predefined as adverse events of special interest (AESIs). Please refer to Section 8.3 for details on AEs requiring additional data collection and events for adjudication.

8.3.8 Technical complaints

Technical complaints will be collected for all products listed on the technical complaint form on a continuous basis. Follow up should be made regularly during the intervention period, to make sure all technical complaints are captured.

Instructions for reporting technical complaints can be found in Appendix 6 (Section 10.6).

In order for Novo Nordisk to perform a complete investigation of reported SAEs, Novo Nordisk might ask the investigator to complete a technical complaint form.

8.4 Pharmacokinetics

Blood samples will be collected to evaluate the pharmacokinetics (PK) of ziltivekimab. PK serum samples will be collected at the visits outlined in the flowchart (Section 1.2) The investigator must record the exact time and date for drawing the blood samples on the laboratory requisition form.

Procedures for sampling, handling, storage, labelling, and shipments of the specimens must be performed in accordance with the laboratory manual.

Bioanalysis of ziltivekimab samples will be performed at a special laboratory (Attachment I) using a validated immunoassay specific for ziltivekimab. A randomisation list will be provided to the special laboratory. The exact method will be described in a bioanalytical report, and the bioanalytical report must be provided before finalisation of the CSR.

The PK samples will be stored and used for anti-drug antibody analysis in case of suspected hypersensitivity reaction, if relevant for overall PK / PD assessment or if requested by Health Authorities. Genetic analyses will not be performed on the samples. The confidentiality of study participants will be maintained.

The samples will be stored at Novo Nordisk or a biorepository assigned by Novo Nordisk after end of study and until marketing authorisation approval or until the research project terminates, but no longer than 15 years from the end of study after which they will be destroyed (refer to

Section 10.7.2. Local requirements may apply. China: see country/region-specific requirements (Appendix 11, Section 10.11).

8.5 Pharmacodynamics

hs-CRP is a biomarker of inflammation and will be used for pharmacodynamic (PD) assessments of ziltivekimab.

Blood samples for determination of plasma concentrations of serum hs-CRP will be drawn as specified in the flowchart (Section 1.2). Procedures for sampling, handling, storage, labelling, and shipments of the specimens must be performed in accordance with the laboratory manual. Bioanalysis of hs-CRP samples will be performed at a special laboratory (Attachment I).

IL-6 levels will be assessed at baseline (visit 2) and analysed at the central laboratory.

8.6 Immunogenicity assessments

8.6.1 Assessments in case of suspicion of hypersensitivity reactions to the product

In case of suspicion of a severe systemic hypersensitivity reaction[53] (i.e., not mild/moderate local reactions) to the investigational product, the participant must be discontinued from study intervention but should remain in the study (Section 7.1.1).

The event must be reported according to Section 8.3.

Digital pictures

It is recommended that the investigator or the participant take digital pictures of the affected area at time of suspicion of hypersensitivity reactions, using any device available (mobile phone, camera etc.) and thereafter as often as judged necessary by the investigator.

The pictures should include subject ID, date and time, time after dosing and a ruler for scaling. All pictures must be stored as part of source documentation at site. Detailed guidance will be provided to a site in case of suspicion of a severe systemic hypersensitivity reaction.

Additional blood samples and other tests

In the event of a **systemic** hypersensitivity reaction, as judged by the investigator, a blood sample is recommended to be drawn as soon as possible, and no later than 12 hours after the reaction.

The following parameters will be analysed:
- Tryptase.
- Total IgE.
- Anti-ziltivekimab IgE antibodies.
- Anti-ziltivekimab binding antibodies.

The PK samples will be used for anti-drug antibody analysis in case of suspected hypersensitivity reaction.

Blood sampling should be repeated in the period 1 to 4 weeks following the systemic hypersensitivity reaction. Furthermore, testing should, if possible, also be performed on samples drawn prior to first administration of study intervention.

Procedures for sampling, handling, storage, labelling, and shipments of the specimens must be performed in accordance with the laboratory manual.

Analysis will be performed by Novo Nordisk or a Novo Nordisk appointed special laboratory (please refer to Attachment I). The results will be reported in a separate report and attached to the CSR.

The PK samples will be stored at Novo Nordisk or a biorepository assigned by Novo Nordisk after end of study and until marketing authorisation approval or until the research project terminates, but no longer than 15 years from the end of study after which they will be destroyed. For retention of residual hypersensitivity samples, please refer to Appendix 7 (Section 10.7.3).

8.7 Genetics

Blood samples for future DNA/RNA/epigenetic analysis will be collected from participants who have consented to participate in the genetic analysis component of the study. Participation in the genetic research is optional and requires separate informed consent. Participants who do not wish to participate in the genetic research may still participate in the study.

Samples will be collected according to the flowchart, Section 1.2. In the event of sample handling failure, a replacement genetic blood sample may be requested from the participant. Refer to Appendix 5 (Section 10.5) for further details.

The specimens collected for optional genomic research will be used to identify or validate genetic markers that may increase our knowledge and understanding of ziltivekimab and of the biology of inflammatory, cardiometabolic, kidney and other related diseases and to study the association of genetic markers with disease pathogenesis, progression and/or treatment outcomes, including efficacy, AEs, and the processes of drug absorption and disposition. These specimens may be used also to develop biomarker or diagnostic assays and establish the performance characteristics of these assays. The collection and analysis of optional genomic specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualised drug therapy for participants in the future. Refer to Appendix 7 (Section 10.7.1) for further details on retention of human biosamples.

Local requirements may apply. Brazil, China, Colombia, Finland, Israel, South Africa, South Korea: see country/region-specific requirements (Appendix 11, Section 10.11).

8.8 Biomarkers

Efficacy biomarkers

Collection of samples for efficacy biomarkers research is part of this study (Section 8.1.1 and Appendix 2, Section 10.2). The following samples are required and will be collected from all participants in this study: blood, in accordance with the flowchart (Section 1.2) and the laboratory manual.

Biosamples for future research

Collection of blood samples for exploratory biomarker investigation for research and hypothesis generation is also part of this study. No clinical decision can be made based on exploratory data. Participation in the biobank component is optional and requires separate informed consent. Study participants who do not wish to participate in the biobank component may still participate in the study. For the biobank, samples will be collected according to the flowchart (Section 1.2) and stored for future analysis.

The samples are collected for the purpose of allowing future analyses of circulating biomarkers when new knowledge or improved measurement techniques may have become available. The analyses may include biomarkers currently known or discovered in the future. Analyses of circulating biomarkers may include analysis of hormones, metabolites or other nongenetic plasma or serum parameters with the purpose of understanding and predicting response to ziltivekimab as well as to increase understanding inflammatory, cardiometabolic, kidney and other related diseases.

The biosamples will be stored at a central laboratory, at a central storage facility or an analysing laboratory contracted by Novo Nordisk for up to 15 years after end of the study (Appendix 7, Section 10.7).

Only relevant Novo Nordisk, consultants, auditors, research organisations or laboratories working for or collaborating with Novo Nordisk as well as storage facility employees will be able to access the stored biosamples and associated data. The biosamples may be transferred to other countries for analysis and will be destroyed at the latest 15 years after end of the study. Novo Nordisk will ensure that third party collaborators live up the regulations on data protection (Appendix 1, Section 10.1.5).

Analysis will be done on the biosamples and associated data (data relating to the test results or results from the main study). The analyses are likely to be performed after the study has come to an end, and results will therefore not be part of the CSR.

The participant may request the stored biosamples for future research to be destroyed by withdrawing the designated informed consent at any timepoint during and after the study. For samples that have already been analysed, the results can still be used for scientific research and will not be removed from the datafile.

Local requirements may apply. Brazil, China, Colombia, Finland, Israel, Norway, South Africa, South Korea; see country/region-specific requirements (Appendix 11, Section 10.11).

8.9 Demography and other baseline assessments

Demographic data are to be recorded in the eCRF at screening (visit 1) and consisted of:

- Date of birth (according to local regulation).
- Sex.
- Race (according to local regulation).
- Ethnicity (according to local regulation).

Race and ethnicity must be self-reported by the participant.

It must be recorded at screening (visit 1) whether female participants are of childbearing potential (see Appendix 4, Section 10.4.1 for details). A female participant is considered fertile following menarche and until becoming postmenopausal unless permanent sterile. If fertility is unclear (e.g., amenorrhea in adolescents or athletes), and a menstrual cycle cannot be confirmed before first dose study intervention, additional evaluation should be considered.

Local requirements may apply. Czech Republic, France, Germany, Hungary, Lithuania, Netherlands, Portugal, Spain, Taiwan: see country/region-specific requirements (Appendix 11, Section 10.11).

8.10 Tobacco and nicotine products use

Tobacco and nicotine products use is to be recorded at baseline and end of treatment, as defined in the flowchart (Section 1.2). Tobacco use/smoking is defined as smoking at least one cigarette or equivalent daily.

8.11 Health economics

Health economics data, associated with medical encounters, will be collected for all participants throughout the study. Hospitalisations will be recorded in the eCRF by the investigator and site staff. Answers to the EQ-5D-5L questionnaire will entered by the study participant using the study app. Protocol-mandated procedures, tests and encounters are excluded.

The data collected may be used to conduct exploratory economic analyses and will include:

- Hospitalisations (see Section 8.1.4.1 for details)
- EQ-5D-5L

8.11.1 EQ-5D-5L

The EuroQoL five dimensions five level (EQ-5D-5L) questionnaire will be used to estimate the impact on participants' health-related quality of life and provides a description of participant's problems by dimensions (descriptive system), a score for overall self-rated health based on a visual analogue scale (VAS) as well as an index score (EQ-5D-5L index) derived from the descriptive system and a population-specific value set.

The EQ-5D index score ranges from 0 to 1 (negative values are allowed for very severe health states) and the EQ-5D-VAS scale ranges from 0 to 100. A higher score indicates better self-reported health status.

Participants should be given the opportunity to complete the questionnaires by themselves without interruption. The questionnaires should be completed in close relation to the visits, prior to or at the visit. Planned time points for the EQ-5D-5L are provided in the flowchart (Section 1.2). Participants should complete the questionnaire using the study app. Participants are not allowed to answer the questions on paper.

Completed EQ-5D-5L questionnaires must be reviewed by the investigator, and the review must be documented in the medical records. If clarification of entries or discrepancies in the questionnaires is needed, the participant must be questioned, and a conclusion made in the participant's source

documents. Care must be taken not to bias the participant. In case of detection of AEs, this should be reported as applicable.

8.12 Patient engagement tools

Three optional engagement tools will be offered to patients during the study, to provide Novo Nordisk with feedback directly from the participants. The patient feedback will allow Novo Nordisk to continuously improve the efforts to improve the participant´s experience and enhance retention.

8.12.1 Subject Participation Feedback Questionnaire (SPFQ)

Study participants will be invited to complete a three-part questionnaire, based on the TransCelerate Subject Participation Feedback Questionnaire (SPFQ). The feedback will allow Novo Nordisk to continuously learn and improve the participants´ experience and enhance retention. The questionnaire is optional, is completed using the study app, and will be offered at selected visits as defined in the flowchart (Section 1.2). Participants are not allowed to answer the questions on paper.

Data from the questionnaires will not be available for the site staff and will not be transferred to the study database.

8.12.2 Study Check-In (SCI)

Study participants will be invited to complete a short visual analogue scale (VAS) assessment to evaluate their engagement and motivation in the study. The purpose of the assessment is to help the investigator assess how the participants feel about their ongoing participation in the study and identify any participants at risk of retention issues. The assessment is optional, is completed using the study app, and will be offered at selected visits as defined in the flowchart (Section 1.2). Participants are not allowed to complete the assessment on paper.

Data from the SCI assessment will not be transferred to the study database.

8.12.3 CardioSignal app

Study participants, with no history of permanent atrial fibrillation, will be invited to use a digital biomarker and monitoring solution, the CardioSignal app (‘MyCardioSignal‘ in the United States). Note, this option is only available for selected countries (i.e., Austria, Belgium, Denmark, Finland, France, Germany, India, Italy, Ireland, Spain, the United Kingdom, and the United States) based on registration status.

Use of the CardioSignal app is optional and requires signing a separate agreement form (Appendix 1, Section 10.1.3). Participants who do not wish to use the CardioSignal app may still participate in the study. For participants who have provided their consent to use the CardioSignal app, their data collected in the app will be used for future research by Precordior (the company who developed the app).

The CardioSignal technology is an app available for modern smartphones (iPhones & Android phones). The app uses the motion sensors in the phone to collect heart muscle movements and is combined with a cloud-based data analysis system. Participants should download the CardioSignal app to their own smartphones. Participants who do not have a suitable smartphone will be provided

with a device on which the CardioSignal app can be downloaded. Participants should receive training in its use by the investigator or delegated site staff before collecting any data.

The CardioSignal application is a CE-marked medical device (class IIa) which is currently approved to detect signs suggestive of atrial fibrillation in the adult population. The objective of offering a digital solution stimulate patient and physician engagement, support retention and adherence and provide a convenient monitoring solution to patients. The potential future benefit may be the identification of a useful non-invasive device to detect and monitor HF and other relevant CV condition.

The app should be used in accordance with the CardioSignal manual. The participants should use the app between visits, in accordance with agreements between the participant and investigator. If signs suggesting atrial fibrillation are detected in consecutive measurements, the participant should consult his/her care provider or the investigator for further evaluation. Relevant findings from the app should be discussed with the participant in relation to all planned and unplanned visits (as defined in the flowchart, Section 1.2), and appropriate actions should be taken at the discretion of the investigator.

Findings must be recorded as adverse events if fulfilling the predefined criteria (Section 10.3) and within the predefined timelines for AE reporting (Section 10.3.5). Events diagnosed as atrial fibrillation, i.e., supraventricular tachyarrhythmia with uncoordinated atrial electrical activation, is defined as an AEs requiring additional data collection on a specific event form (Section 8.3, Table 8-1). Medication administered as part of standard of care treatment of atrial fibrillation, should be recorded as concomitant medication (Section 6.8.1).

Data collected in the CardioSignal app will not be part of the CSR.

9 Statistical considerations

The statistical analysis plan (SAP) will be finalised prior to any interim testing, and it will include a more technical and detailed description of the statistical analyses and interim analysis described in this section. To protect study integrity, further statistical details of the interim testing is deferred to the SAP. This section is a summary of the planned statistical analyses of the most important endpoints including primary and confirmatory secondary endpoints. Novo Nordisk will perform the statistical analyses except interim testing (Section 9.4).

The analysis and reporting will be done after the global end of the study.

9.1 Statistical hypotheses

Let HR denote the hazard ratio between ziltivekimab and placebo for a time-to-event endpoint.

The primary hypothesis to be tested is that ziltivekimab is superior to placebo in terms of the primary estimand. The null hypothesis will be tested against the one-sided alternative hypothesis:

H_0: HR$\geq$ 1.0 against H_A: HR<1.0.

For the secondary estimands with the confirmatory secondary time-to-event endpoints, the above hypothesis will be tested similarly. For the confirmatory secondary endpoint of CV death and HF events (HF hospitalisation or urgent HF visit), let MR denote the ratio of the mean number of events between ziltivekimab and placebo. The following null hypothesis will be tested against the one-sided alternative hypothesis:

H_0: MR$\geq$ 1.0 against H_A: MR<1.0.

9.1.1 Multiplicity adjustment

The hypotheses will be tested under the control of a study-wise type I error rate of 2.5% (one-sided) using prespecified alpha spending functions for the primary and confirmatory secondary endpoints.

To control the study-wise type I error for multiplicity, a prespecified hierarchical testing strategy will be used. The first confirmatory secondary hypothesis in the hierarchy will only be tested if superiority is concluded for the primary hypothesis. The second confirmatory secondary hypothesis will only be tested if superiority is concluded for the previous hypothesis.

The hierarchy for the hypotheses corresponds to the following order of the confirmatory endpoints:
1. Time to first CV death or HF hospitalisation or urgent HF visit.
2. Time to first expanded composite HF endpoint.
3. Number of CV deaths and HF hospitalisations or urgent HF visits (first and recurrent).
4. Time to CV-death.
5. Time to all-cause death.

Multiplicity adjustment due to an interim analysis is detailed in Section 9.4.

9.2 Analysis sets

For the purposes of analysis, one analysis set is defined, the full analysis set (FAS) (Table 9-1).

Table 9-1 Analysis populations

Participant analysis set	Description
Full analysis set (FAS)	All participants randomised.

In exceptional cases, participants or observations may be eliminated from the full analysis set. In such case the reasons for their exclusion will be documented before unblinding. The participants and observations excluded from analysis sets, and the reason for this, will be described in the CSR.

Study participants will be analysed according to the randomised treatment. Observations will be included in the analysis regardless of discontinuation of randomised treatment and any other intercurrent event

A participant is considered lost to follow-up (LTFU) if the participant does not complete the study and does not withdraw consent.

The in-study observation period for a participant is defined as the period from date of randomisation to the first of (both inclusive):

- date of follow-up visit.
- date when participant withdrew consent.
- date of last contact with participant (for participant LTFU).
- date of death.

9.3 Statistical analyses

9.3.1 General considerations

For confirmatory endpoints controlled for multiplicity, estimated treatment effects will be presented together with two-sided 95% confidence intervals and one-sided p-values for test of the hypotheses. For reporting of results, the estimated treatment effect and the 95% confidence interval will be accompanied by the two-sided p-value.

Missing data are defined as data that are planned to be collected and could have been collected but are not present in the database. This implies that data that are structurally missing due to death or administrative censoring (end of study) are not considered missing.

Statistical analyses of all confirmatory endpoints are based on the FAS using the in-study observation period.

9.3.2 Primary endpoint analysis

9.3.2.1 Definition of endpoint

The primary endpoint is time to first occurrence of a composite HF endpoint consisting of CV death, HF hospitalisation or urgent HF visit.

The endpoint is based on EAC-confirmed events, and any undetermined cause of death is included as a CV death. The date of death to be used in the analyses is the EAC established date of death. Hospitalisations should be delineated from urgent visits (confirmed as part of the adjudication process) in order for the event to be classified as one event of either hospitalisation or urgent visit.

The date of the event is the date of admission for hospitalisations and the date of the visit for urgent visits.

9.3.2.2 Main analytical approach

To test the primary hypothesis (Section 9.1), the hazard ratio of the primary endpoint comparing ziltivekimab versus placebo will be estimated from a Cox proportional hazards model with treatment group (ziltivekimab, placebo) as fixed factor together with the two-sided 95% confidence interval and one-sided fixed design p-value for hypothesis testing. The score test from the Cox model will be used for testing. Superiority of ziltivekimab versus placebo will be considered confirmed if the associated null hypothesis is rejected based on a nominal significance level derived from the alpha spending function.

The intercurrent event of non-CV death will be handled by the while alive strategy and thus treated as censored in the Cox analysis. The underlying assumption in the analysis is missing at random. Data missing due to lost-to-follow-up or withdrawal of consent is also assumed to be missing at random and will be handled by censoring.

Study participants will be analysed according to the randomised treatment, i.e., using the FAS (Section 9.2).

9.3.2.3 Sensitivity analysis

The primary analysis assumes independent censoring for participants who have withdrawn consent or are lost to follow-up. To investigate the impact of this assumption on the results of the primary analysis, a 2-way tipping point analysis based on the approach described in Zhao et al.[55] is performed.

9.3.2.4 Supplementary analysis

Supplementary analysis of the primary endpoint will be detailed in the SAP.

9.3.3 Secondary endpoints analysis

Confirmatory secondary endpoints

The confirmatory secondary time to event endpoints, will be analysed using the same Cox proportional hazards model used to analyse the primary endpoint.

The confirmatory secondary endpoint of number CV deaths and HF events (HF hospitalisation or urgent HF visit) will be analysed using a marginal mean regression model for recurrent events accounting for competing risk of dying.[56, 57] Treatment effect is reported as a mean ratio and corresponding 95% robust confidence interval to account for the dependency of recurrent events within-patient.

Superiority of ziltivekimab versus placebo will be considered confirmed if the associated null hypothesis is rejected based on the hierarchical testing and the nominal significance level derived from the alpha spending function.

Sensitivity analyses for the confirmatory secondary endpoints will only be made if superiority is confirmed for the individual endpoint. The sensitivity analyses will address intercurrent events and impact of missing data and will be detailed in the SAP.

Supportive secondary endpoints

Details on analyses of additional supportive secondary endpoints will be described in the SAP.

9.3.4 Exploratory endpoint analysis

Details on analyses of the exploratory endpoint will be described the SAP.

9.3.5 Other safety analyses

All safety analyses will be made on the full analysis set. The standard safety assessments (AEs, safety laboratory parameters, vital signs, etc.) will be reported descriptively, including any notable changes of clinical interest in laboratory parameters.

9.3.6 Other analyses

For other analyses, please refer to the SAP.

9.3.7 Pharmacokinetic and pharmacodynamic modelling

Ziltivekimab serum concentration data will be used for population PK analysis. The objective of the population PK analysis is to evaluate the effects of prespecified covariates on serum concentrations of ziltivekimab.

A more technical and detailed elaboration of the population PK analysis will be given in a modelling analysis plan (MAP), which will be prepared before database lock (DBL). In brief, the one-compartment PK model with first order absorption and first order elimination developed for ziltivekimab in the RESCUE-US phase 2 study will be used as a basis for the analysis. The same structural model will be used and the absorption rate constant (K_a) in the model will be fixed to the value obtained in the RESCUE-US study, whereas clearance (CL/F) and volume of distribution (V/F) will be estimated (with between-patient variability included on both parameters). The covariates of interest will be incorporated into the PK model using criteria which will be specified in the MAP.

The population PK analysis will be reported in a separate modelling report, which will not be part of the CSR. The individual ziltivekimab serum concentration data will be tabulated in the bioanalytical report.

9.4 Interim analysis

Before end of recruitment period, a blinded evaluation of the event rate in the study may be performed by Novo Nordisk/the steering committee (StC) to assess whether the assumptions on event rate remain valid. The evaluation will be based on blinded tabulations of event rates, baseline characteristics and concomitant medications (i.e., not split into ziltivekimab and placebo groups). This evaluation will allow for modifications of the sample size and recruitment period, to ensure reliable assessments of the effects of ziltivekimab.

A formal interim testing is prespecified but may be reconsidered during the study period.

Interim testing will be based on efficacy stopping boundaries for the primary endpoint. To strongly control the study-wise one-sided type I error rate of 2.5%, alpha spending functions are used for the primary and all the confirmatory secondary endpoints. Additionally, a nonbinding futility stopping boundary will be applied for the primary endpoint.

Interim testing will be performed based on a locked dataset at the testing time-point by a statistical vendor independent of study conduct and external to Novo Nordisk.

The data monitoring committee (DMC) is an independent, external committee composed of members whose expertise covers relevant specialties including statistics (see Appendix 1, Section 10.1.6.2 for details). Information regarding responsibilities, procedures and workflow to be used by the DMC are specified in the DMC charter. The DMC evaluates the unblinded data using the stopping boundaries from the alpha spending functions as guidance and makes the decision to recommend early study termination.

If the study is terminated early following an interim testing, final analyses will be performed based on all events from the in-study observation period including events collected after interim time-point, referred above.

To protect study integrity, no further details of interim testing is described in the protocol. These details, including timing of interim, type I and II error rate control by alpha spending functions for the primary and confirmatory secondary endpoints in the hierarchical testing strategy will be prespecified and described in detail in the SAP.

9.5 Sample size determination

Power for primary estimand

The study is designed using the group sequential design with 90% power to confirm superiority using a study-wise type I error rate of 2.5% (one-sided) for the primary estimand. Using a randomisation ratio of 1:1 and assuming a true HR of 0.80 a total of 845 primary endpoint events are required. With this number of primary endpoint events, the power as a function of the true HR can be seen in Figure 9-1.

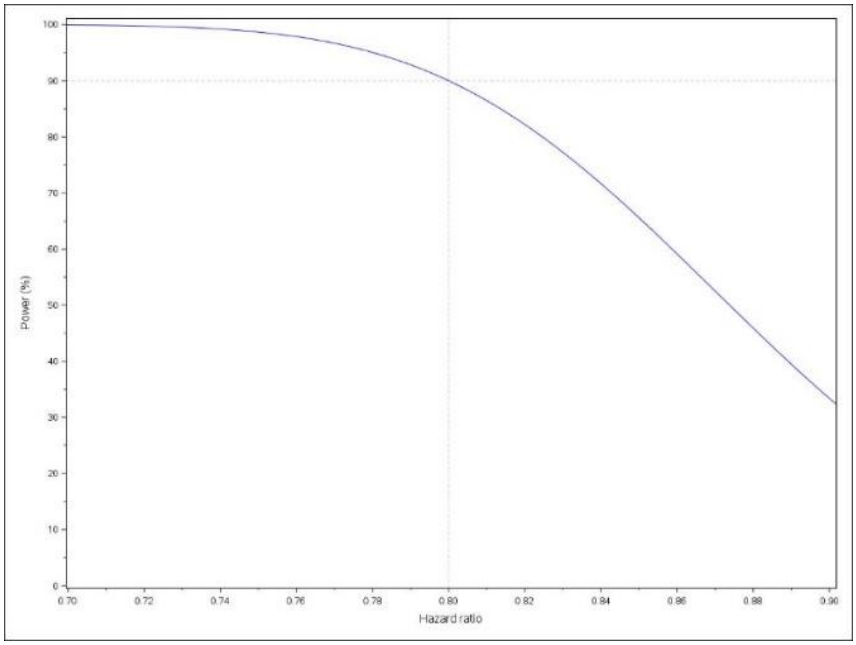
For calculation the number of randomised participants needed the following is assumed:

- annual primary endpoint rate in the placebo group of 7.8%.
- annual rate of lost to follow-up, withdrawal, and non-CV death of 3.5%.
- uniform recruitment occurs in 36 months.
- study duration is up to 4 years.

The assumptions on annual event rate and non-CV death are based on EMPEROR-preserved[58] (annual event rate for primary endpoint was 6.9% in the active group and 8.7% in the placebo group) and assuming that up to half of the participants are using SGLT2 inhibitors.

Under these assumptions, it is estimated that 5,558 participants are needed to accrue 845 events within the anticipated study timelines. Due to the uncertainties in the event-rate, approximately 5,600 participants will be randomised.

Figure 9-1 Power as a function of the true hazard ratio



Power for secondary estimands

If superiority is confirmed for the primary estimand the confirmatory secondary estimands will be tested through a hierarchical testing strategy. The marginal powers below are calculated under the assumptions that the study continues to the final analysis and a full 2.5% one-sided significance is used. The assumed event rates are based on the event rates seen in EMPEROR-preserved and PARAGON-HF and the same considerations regarding SGLT2 inhibitor use as for the primary estimand.[58, 59]

The marginal power for superiority in favour of ziltivekimab for the estimand with 4-point expanded composite HF endpoint is 93%, based on an assumed hazard ratio of 0.8 and an annual event rate of 8.5% in the placebo group.

The marginal power for superiority in favour of ziltivekimab for the estimand with CV death and HF endpoint (number of CV deaths and HF hospitalisations or urgent HF visits), is expected to be similar or larger than the power for the primary endpoint, as it is based on recurrent events of the events included in the primary endpoint.

The marginal power for superiority in favour of ziltivekimab for the estimand with CV death endpoint is 62%, based on an assumed hazard ratio of 0.8 and an annual event rate of 3.6% in the placebo group.

The marginal power for superiority in favour of ziltivekimab for the estimand with all-cause mortality endpoint is 32%, based on an assumed hazard ratio of 0.9 and an annual event rate of 6.6% in the placebo group.

10 Supporting documentation and operational considerations

10.1 Appendix 1: Regulatory, ethical, and study oversight considerations

Local requirements may apply. Bulgaria, China: see country/region-specific requirements (Appendix 11, Section 10.11).

10.1.1 Regulatory and ethical considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki[60] and applicable ICH Good Clinical Practice (GCP) Guideline.[61]
- Applicable laws and regulations.

The protocol, informed consent forms, investigator's brochure (as applicable) and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC and reviewed and approved by the IRB/IEC before the study is initiated.

Regulatory authorities will receive the clinical trial application, protocol amendments, reports on SAEs, and the CSR according to national requirements.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate safety hazard to study participants.

Before a site is allowed to start screening potential participants, written notification from Novo Nordisk must be received.

The investigator will be responsible for:

- providing written summaries of the status of the study annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC and/or regulatory authorities.
- notifying the IRB/IEC of SAEs or other relevant safety findings as required by IRB/IEC procedures.
- providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations.
- ensuring submission of the CSR synopsis to the IRB/IEC.
- reporting any potential serious breaches to the sponsor immediately (within 24 hours after discovery). A serious breach is a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of data generated in the clinical study. This includes persistent or systematic non-compliance with ICH GCP E6 and/or the protocol.

Local requirements may apply. Japan, Mexico, Slovakia, US: see country/region-specific requirements (Appendix 11, Section 10.11).

10.1.2 Financial disclosure

Investigators and sub-investigators will provide Novo Nordisk with sufficient, accurate financial information as requested to allow Novo Nordisk to submit complete and accurate financial

certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and one year after completion of the study.

For US sites, verification under disclosures per Code of Federal Regulations (CFR) of Financial Conflict of Interest applies.

10.1.3 Informed consent process

The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study. This includes the use of an impartial witness where required according to local requirements.

The investigator must ensure the participant ample time to come to a decision whether or not to participate in the study.

Study participants must be informed that their participation is voluntary. Study participants must be informed about their privacy rights. Participants will be required to sign and date a statement of informed consent ('Agreement to take part' form) that meets the requirements of local regulations, ICH GCP[61] guidelines, Declaration of Helsinki,[60] privacy and data protection requirements, where applicable, and the IRB/IEC or site.

The medical record must include a statement that written informed consent was obtained before any study-related activity and the date when the written consent was obtained. The authorised person obtaining the informed consent must also sign and date the informed consent form before any study-related activity.

The responsibility of seeking informed consent must remain with the investigator, but the investigator may delegate the task to a medically qualified person, in accordance with local requirements.

Study participants must be re-consented to the most current version of the informed consent forms during their participation in the study according to sponsors instructions.

A copy of the informed consent forms must be provided to the participant.

Separate informed consent forms are available for various other situations. Informed consent must be obtained before activities related to these are undertaken:

- Direct shipment of study intervention to the participants (Section 6.2.5).
- Use of CardioSignal app (Section 8.12.3). Note, this option is only available for selected countries based on registration status. The investigator must explain to each participant the objectives of the use of the app. Study participants must be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study period.
- Male partner of a female participant in case of an abnormal pregnancy (Appendix 4, Section 10.4.3).
- Biosamples for future analysis (genetics and biomarkers):

- Genetic testing (Appendix 5, Section 10.5). The investigator must explain to each participant the objectives of the genetic testing. Participants must be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study period.
- Long-term storage of human samples and the use of samples for optional exploratory research (Appendix 7, Section 10.7). The investigator must explain to each participant the objectives of the exploratory research. Study participants must be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

Local requirements may apply. Brazil, Taiwan: see country/region-specific requirements (Appendix 11, Section 10.11).

10.1.4 Recruitment and information to participants during the study

Materials will be provided to sites to assist them in identifying and recruiting patients, including advertisements and information for patients and their family, support structure, and any referring physicians. Materials will be translated and approved according to local procedures for use at the discretion of the site.

The site will be offered a communication package for the participant during the conduct of the study. The package content is issued by Novo Nordisk. The communication package will contain written information intended for distribution to the participants. The written information will be translated and adjusted to local requirements and distributed to the participant at the discretion of the investigator. The participant may receive a “welcome to the study letter” and a “thank you for your participation letter” after completion of the study. Further, the participant may receive other written information during the study.

Different initiatives for participant motivation and engagement, to support retention, will be implemented throughout this study (Section 8.12). Materials and items will be supplied if locally acceptable. The retention items will be relevant for the participants’ participation in the study and will not exceed local fair market value.

Updated reports tracking relevant parameters related to the health of each patient are available for site staff to share and discuss with the patient throughout the study. This will enable the patients to better understand their general health, their heart disease and the progress made during the study and thereby qualify them to be an active participant in their care.

All written information to participants must be sent to IRB/IEC for approval/favourable opinion and to regulatory authorities for approval or notification according to local regulations.

10.1.5 Data protection

Participants will be assigned a 7-digit unique identifier, a subject ID. Any participant records or datasets that are transferred to Novo Nordisk will contain the identifier only. No direct identifiers from the participant are transferred to Novo Nordisk.

The participant and any biological material obtained from the participant will be identified by subject ID, visit number and study ID. Appropriate measures such as encryption or leaving out

certain identifiers will be enforced to protect the identity of participants as required by local, regional and national requirements.

The participant must be informed about his/her privacy rights, including that his/her personal study-related data will be used by Novo Nordisk in accordance with local data protection law. The disclosure of the data must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by auditors or other authorised personnel appointed by Novo Nordisk, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Personal data may be collected from participants due to process requirements from Novo Nordisk's suppliers. This data is needed to ensure that the relevant data analysis for the study can be performed but will not be part of the data transferred to Novo Nordisk, the assessment of the study endpoints or the clinical study report. A list of any such data values must be kept as part of the study documentation along with an explanation of why it was required.

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 organisational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorised disclosure or access.

Local requirements may apply. Denmark, UK: see country/region-specific requirements (Appendix11, Section 10.11).

10.1.6 Committees structure

10.1.6.1 Novo Nordisk safety committee

Novo Nordisk will perform ongoing safety surveillance. If new safety signals are identified, these will be evaluated by an internal safety committee. The safety committee may recommend unblinding of any data for further analysis, and in this case an internal study independent *ad hoc* group will be established in order to maintain the blinding of the study personnel.

10.1.6.2 Data monitoring committee

A data monitoring committee (DMC) will be established for this study. The DMC is an independent, external committee composed of members whose expertise covers relevant specialties including statistics. The DMC is established to review and evaluate accumulated data from the study at predefined time points as well as *ad hoc*.

Blinded and unblinded data analyses during study conduct will be performed by the DMC, as described in the DMC charter. Study integrity will be ensured by using a statistician independent of study conduct and external to Novo Nordisk to prepare data for the DMC.

The DMC will provide recommendations on study continuation, modification or termination. Based on accumulated data, the DMC will make recommendations regarding the ongoing conduct of the study in order to protect the safety of the participants and to ensure an acceptable benefit/risk ratio for participants enrolled in the study.

Furthermore, the DMC evaluates the unblinded interim testing using the group sequential stopping boundaries as guidance. Stopping the study is allowed if the stopping boundaries are crossed and the DMC makes the decision to recommend early study termination.

Information regarding responsibilities, procedures and workflow to be used by the DMC are specified in the DMC charter.

10.1.6.3 Steering committee

A steering committee (StC) will provide scientific and operational leadership for the study. The committee will consist of experts from outside Novo Nordisk, and designated Novo Nordisk employees. The committee will operate under a charter agreed with Novo Nordisk.

10.1.6.4 Event adjudication committee

The EAC is an independent, external committee composed of members covering all relevant medical specialities. The EAC is established to perform ongoing blinded adjudication of selected events (Table 8-1 and Appendix 8, Section 10.8). The EAC will have no authority to impact study conduct, study protocol or amendments.

The EAC is an independent, external committee composed of permanent members covering all required medical specialities. EAC members must disclose any potential conflicts of interest and must be independent of Novo Nordisk

The EAC will evaluate predefined source documents collected by site staff, by using predefined definitions and guidelines. Information regarding EAC member responsibilities, adjudication procedures and event definitions to be used by the EAC are specified in the EAC charter.

The purpose of the adjudication is to confirm events in a consistent manner according to standardised criteria using independent external medical experts. In this study, cardiovascular events will be adjudicated in order to adequately characterise the cardiovascular effects of ziltivekimab. In addition, events of infections of special interest will be evaluated by adjudication as anti-IL-6 therapies have been associated with the risk of inducing immune suppression and promoting the emergence of infections, sometimes serious in nature. The events for adjudication are listed in Table 8-1.

The assessments made by both the event adjudication committee and the investigator will be evaluated and included in the CSR.

10.1.6.5 Supportive panels

Global expert panel

A global expert panel (GEP) consisting of selected principal investigators, identified as national leaders (NLs) and scientific experts, and a small number of expert national study coordinators will

be formed. The panel members will discuss and advise on global and local operational issues related to study conduct including participant recruitment, retention and protocol adherence. The panel will operate under a charter agreed with Novo Nordisk. National leaders that are not part of the GEP may be appointed in some countries.

National study coordinators

For each country/region participating in the study, where it is appropriate, a national study coordinator (NSC) will be selected. The NSCs will provide operational input to participant recruitment, retention and adherence related topics. The NSCs will operate under a charter agreed with Novo Nordisk.

10.1.7 Dissemination of clinical study data

Study information will be disclosed at clinicaltrials.gov, euclinicaltrials.eu and novonordisk-trials.com and if applicable, also on other national or regional study registries. It will be disclosed according to applicable requirements, relevant recommendations or regulations, such as the Declaration of Helsinki[60], the International Committee of Medical Journal Editors (ICMJE)[62], the Food and Drug Administration Amendment Act (FDAAA)[63], European Commission Requirements[64-66] and in accordance with Novo Nordisk commitment to clinical transparency. If a participant requests to be included in the study via the Novo Nordisk e-mail contact at these web sites, Novo Nordisk may disclose the investigator's contact details to the participant. As a result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations. China: see country/region-specific requirements (Appendix 11, Section 10.11).

10.1.8 Data quality assurance

10.1.8.1 Case report forms

Novo Nordisk or designee is responsible for the data management of this study including quality checking of the data.

To demonstrate his/her oversight of the collected data, the investigator should sign the electronic CRF (eCRF) on a regular basis during the conduct of the study as well as at the end of the study.

All participant data relating to the study will be recorded on eCRFs unless transmitted electronically to Novo Nordisk or designee (e.g., laboratory data and ePRO questionnaires). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF and for ensuring that all relevant questions are answered, and that no empty data field exists. If a test or an assessment has not been done and will not be available, or if the question is irrelevant (e.g., is not applicable), indicate this by choosing the appropriate option. Free-text comments are discouraged.

The following will be provided as paper CRFs:

- Pregnancy forms.

The following will be provided as back-up paper CRFs to be used when access to the eCRF is revoked or the eCRF is temporary unavailable:

- AE forms.
- Safety information forms.
- Technical complaint forms (also to be used to report complaints on study intervention not yet allocated to a participant).

Corrections to the CRF data may be made by the investigator or the investigator's delegated staff. An audit trail will be maintained in the CRF application containing as a minimum: the old and the new data, identification of the person entering the data, date and time of the entry and reason for the correction. If corrections are made by the investigator's delegated staff after the date when the investigator signed the CRF, the CRF must be signed and dated again by the investigator.

The investigator must ensure that data is recorded in the CRF as soon as possible, preferably within 5 working days after the visit. Once data has been entered, it will be available to Novo Nordisk for data verification and validation purposes.

10.1.8.2 Monitoring

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents (original documents, data and records). Remote access to the source data documents by Novo Nordisk monitors and auditors can be agreed in countries where this is acceptable according to regulatory requirements and national legislation.

Direct access includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are important to the evaluation of the study. If the electronic source data does not have a visible audit trail, the investigator must provide the monitor with signed and dated printouts. In addition, the relevant site staff should be available for discussions at monitoring visits and between monitoring visits (e.g., by telephone).

Study monitors will perform ongoing source data verification of critical data points to confirm that data entered into the eCRFs by authorised site personnel are accurate, complete and verifiable from source documents. Study monitors will perform ongoing source data review to ensure that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP[61], and all applicable regulatory requirements, evaluating the adequacy of critical processes at site for the execution of the protocol, collection of study data, to ensure that the safety and rights of participants are being protected.

Monitoring will be conducted using a risk-based approach including risk assessment, monitoring plans, centralised monitoring (remote assessment of data by Novo Nordisk) and visits to sites.

Quality tolerance limits (QTLs) will be predefined in the relevant monitoring plan to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarised in the clinical study report.

10.1.8.3 Protocol compliance

Deviations from the protocol should be avoided. If deviations do occur, the investigator must inform the monitor without delay and the implications of the deviation must be reviewed and discussed.

Deviations must be documented and explained in a protocol deviation by stating the reason, date, and the action(s) taken. Some deviations, for which corrections are not possible, can be acknowledged and confirmed via edit checks in the eCRF or via listings from the study database.

10.1.9 Source documents

All data entered in the eCRF must be verifiable in source documentation other than the eCRF.

If source data is entered directly in a paper CRF, each data entry or clear series of data entries must be signed and dated separately by the study staff making the entry.

For ePROs, data in the service providers database is considered source data.

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the site. Any source data generated by investigator's subcontractors must be archived and accessible by the site.
Data that is transcribed into the eCRF from source documents must be consistent with the source documents, or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records. Also, current medical records must be available.

It must be possible to verify participant's medical history in source documents, such as participant's medical record.

The investigator must document any attempt to obtain external medical information by noting the date(s) when information was requested, and who was contacted.

Definition of what constitutes source data can be found in a source document agreement at each study site. There will only be one source document defined at any time for any data element.

10.1.10 Retention of clinical study documentation

Records and documents, including signed informed consent forms, pertaining to the conduct of this study must be retained by the investigator for 25 years after end of study unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Novo Nordisk. No records may be transferred to another location or party without written notification to Novo Nordisk.

The investigator/institution should have control of all essential documents and records generated by the investigator/institution before, during, and after the study. The investigator must be able to access his/her study documents without involving Novo Nordisk in any way. If applicable, eCRF and other participant data will be provided in an electronic readable format to the investigator before access is revoked to the system supplied by Novo Nordisk. Site-specific CRFs and other participant data (in an electronic readable format or as paper copies or prints) must be retained by the site. A copy of all data will be stored by Novo Nordisk.

Study participant's medical records must be kept for the maximum period permitted by the hospital, institution or private practice.

Local requirements may apply. China, Spain: see country/region-specific requirements (Appendix 11, Section 10.11).

10.1.11 Study and site start and closure

First act of recruitment

The start of study is defined as the date when the clinical study will be open for recruitment of participants, i.e., the 'first act of recruitment.' The first act of recruitment is defined as the first site activation in the study.

Study or site termination

Novo Nordisk reserves the right to close the site or terminate the study at any time for any reason at the sole discretion of Novo Nordisk. If the study is suspended or terminated, the investigator must inform the participants promptly and ensure appropriate therapy and follow-up. The investigator and/or Novo Nordisk must also promptly inform the regulatory authorities and IRBs/IECs and provide a detailed written explanation.

Sites will be closed upon study completion. A site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed.

The investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a site by Novo Nordisk or investigator may include but are not limited to:

- failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, Novo Nordisk procedures or GCP guidelines.
- inadequate recruitment of participants by the investigator.
- discontinuation of further study intervention development.

Interim testing may allow for premature termination of the study.

10.1.12 Responsibilities

The investigator is accountable for the conduct of the study at his/her site and must ensure adequate supervision of the conduct of the study at the site. If any tasks are delegated, the investigator must maintain a log of appropriately qualified persons to whom he/she has delegated specified study-related duties. The investigator must ensure that there is adequate and documented training for all staff participating in the conduct of the study. It is the investigator's responsibility to supervise the conduct of the study and to protect the rights, safety, dignity and well-being of the participants.

A qualified physician, who is an investigator or a sub investigator for the study, must be responsible for all study-related medical decisions.

The investigator is responsible for filing essential documents (i.e., those documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced) in the investigator trial master file. The documents, including the participant identification code list must be kept in a secure locked facility so that no unauthorised persons can get access to the data.

The investigator will take all necessary technical and organisational safety measures to prevent accidental or wrongful destruction, loss or deterioration of data. The investigator will prevent any unauthorised access to data or any other processing of data against applicable law. This also includes ensuring that no indirect sharing of user credentials for IT systems used in this study takes place (e.g., by not sharing IT equipment with others in a way where user credentials have the possibility of being shared). The investigator must be able to provide the necessary information or otherwise demonstrate to Novo Nordisk that such technical and organisational safety measures have been taken.

During any period of unavailability, the investigator must delegate responsibility for medical care of participants to a specific qualified physician who will be readily available to participants during that time.

If the investigator is no longer able to fulfil the role as investigator (e.g., if he/she moves or retires), a new investigator will be appointed in consultation with Novo Nordisk.

The investigator and other site personnel must have sufficient English skills according to their assigned task(s).

10.1.13 Indemnity statement

Novo Nordisk carries product liability for its products, and liability as assumed under the special laws, acts and/or guidelines for conducting clinical studies in any country/region, unless others have shown negligence.

Novo Nordisk assumes no liability in the event of negligence or any other liability of the sites or investigators conducting the study or by persons for whom the said site or investigator are responsible.

Novo Nordisk accepts liability in accordance with country/region-specific laws, acts and guidelines. Australia, Austria, Belgium, Brazil, France, Mexico, Poland: For any country/region specific indemnity requirements supplementing the above, please refer to country/region-specific requirements (Appendix 11, Section 10.11).

10.1.14 Publication policy

The information obtained during the conduct of this study is considered confidential and may be used by or on behalf of Novo Nordisk for regulatory purposes as well as for the general development of the study intervention. All information supplied by Novo Nordisk in connection with this study shall remain the sole property of Novo Nordisk and is to be considered confidential information.

No confidential information shall be disclosed to others without prior written consent from Novo Nordisk. Such information shall not be used except in the performance of this study.

The information obtained during this study may be made available to other investigators who are conducting other clinical studies with the study intervention, if deemed necessary by Novo Nordisk. Provided that certain conditions are fulfilled, Novo Nordisk may grant access to information obtained during this study to researchers who require access for research projects studying the same disease and/or study intervention studied in this study.

Novo Nordisk may publish on its clinical studies website a redacted CSR for this study.

Two investigators will be appointed by Novo Nordisk to review and sign the CSR (signatory investigators) on behalf of all participating investigators.

10.1.14.1 Communication of results

Novo Nordisk commits to communicate and disclose results of studies regardless of outcome. Disclosure includes publication of a manuscript in a peer-reviewed scientific journal, abstract submission with a poster or oral presentation at a scientific meeting or disclosure by other means.

The results of this study will be subject to public disclosure on external web sites according to international and national regulations. Novo Nordisk reserves the right to defer the release of data until specified milestones are reached, for example when the CSR is available. This includes the right not to release the results of interim testing, because the release of such information may influence the results of the entire study.

At the end of the study, one or more scientific publications may be prepared collaboratively by the investigator(s) and Novo Nordisk. Novo Nordisk reserves the right to postpone publication and/or communication for up to 60 days to protect intellectual property.

In all cases, the study results will be reported in an objective, accurate, balanced and complete manner, with a discussion of the strengths and limitations. In the event of any disagreement on the content of any publication, all StC members or all authors opinions will be fairly and sufficiently represented in the publication.

10.1.14.2 Authorship

Novo Nordisk will work with one or more investigator(s) and other experts who have contributed to the study concept or design, acquisition, analysis or interpretation of data to report the results in one or more publications.

The steering committee (StC)will be responsible for communication of primary study results. This will include appointing the publication group and authorship, overseeing the preparations and final approval of manuscripts and congress communications of study results.

Authorship of publications should be in accordance with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals by the International Committee of Medical Journal Editors.[67]

All authors will be provided with the relevant statistical tables, figures, and reports needed to evaluate the planned publication.

Where required by the journal, the investigator from each study site will be named in an acknowledgement or in the supplementary material, as specified by the journal.

10.1.14.3 Site-specific publications by investigators

For a multicentre clinical study, analyses based on single-site data usually have significant statistical limitations and frequently do not provide meaningful information for healthcare professionals or participants, and therefore may not be supported by Novo Nordisk. Thus, Novo Nordisk may deny a request or ask for deferment of the publication of individual site results until the primary manuscript is accepted for publication. In line with Good Publication Practice, such individual reports should not precede the primary manuscript and should always reference the primary manuscript of the study.

10.1.14.4 Investigator access to data and review of results

As owner of the study database, Novo Nordisk has the discretion to determine who will have access to the database. Individual investigators will have their own research participants' data and will be provided with the randomisation code after results are available.

10.2 Appendix 2: Clinical laboratory tests

All study-required laboratory assessments will be performed by a central laboratory, except urine hCG pregnancy testing, which will be performed locally unless serum testing is required by local regulation or IRB/IEC. Furthermore, ziltivekimab concentrations, anti-ziltivekimab-antibodies and parameters measured in case of suspicion of a severe systemic hypersensitivity reaction[53] will be analysed at a special laboratory (Attachment I).

The tests detailed in Table 10-1 and Table 10-2 will be performed by the central laboratory unless otherwise specified. Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations. Due to the risk of unblinding, local CRP/hs-CRP testing should only be performed if deemed clinically necessary, unless the results are needed for the evaluation and reporting of AEs, as judged by the investigator. Local CRP/hs-CRP results should not be shared actively with the Sponsor or entered into the eCRF unless part of AE reporting. Only laboratory samples specified in the protocol should be sent to the central laboratory for analysis; if additional laboratory sampling is needed, e.g., to follow up on AEs, this must be done at a local laboratory.

Table 10-1 Protocol-required efficacy laboratory assessments

Laboratory assessments	Parameters
Biomarkers	• hs-CRP • Interleukin-6[a] • NT-proBNP • eGFR calculated by the central laboratory based on the creatinine value using the CKD-EPI equation[10],[b]
Biobank (genetics and biomarkers)	• The blood samples are collected for the purpose of allowing additional analyses of genetics and biomarkers at a later point in time when new knowledge or improved measurement techniques may have become available. The analyses may include biomarkers currently known or discovered in the future. • These samples need to be frozen. • The analyses are likely to be performed after the study has come to an end, and results will therefore not be part of the clinical study report. • The biobank samples may be stored up to 15 years after end of the study at a central laboratory.
Glucose metabolism	• HbA1c
Other tests	• Ziltivekimab concentrations[c] • Anti-ziltivekimab antibody[c]

Notes: [a] The baseline sample will be analysed at the central lab using a total IL-6 assay;
[b] For the central laboratory calculation of the eGFR information year of birth will be collected on the laboratory requisition form. 01-Jul of the year of birth will be used for the calculation;
[c] The test will be performed by special laboratory;
Abbreviations: CKD-EPI = chronic kidney disease – epidemiology collaboration; eGFR = estimated glomerular filtration rate; HbA_{1c} =glycated haemoglobin; hs-CRP = high sensitivity C-reaction protein; NT-proBNP = N-terminal-pro-brain natriuretic peptide.

Table 10-2 Protocol-required safety laboratory assessments

Laboratory assessments	Parameters
Haematology	• Erythrocytes • Haemoglobin • Leucocytes • Differential count (eosinophils, neutrophils, basophils, monocytes and lymphocytes) • Thrombocytes • Haematocrit • MCH • MCHC • MCV • Reticulocyte count
Biochemistry[a]	• ALT • Albumin • ALP • AST • Creatinine • Ferritin • Haptoglobin • Potassium • Sodium • Total bilirubin • Transferrin • TSAT
Lipids	• Total cholesterol • HDL cholesterol • Non-HDL cholesterol • LDL cholesterol • Triglycerides
Serology	• HBsAg. • Hepatitis C Ab screen[b]. • anti-HBc • HBV DNA[b].
Tuberculosis	• Latent tuberculosis infection (QuantiFERON-TB Gold)
Pregnancy testing	• Highly sensitive urine hCG pregnancy test (as needed for women of childbearing potential)[c,d].
Other tests	• In case of systemic hypersensitivity (Section 8.6.1): Tryptase, total IgE antibodies, anti-ziltivekimab IgE antibodies, anti-ziltivekimab binding antibodies

Notes: [a] Details of required actions and follow-up assessments for increased liver parameters including any study intervention discontinuation criteria are given in Sections 7.1.1 and Appendix 3, Section 10.3.2 (biochemical components of Hy's Law);
[b] Hepatitis C viral RNA (PCR) testing will be performed if the Hepatitis C Ab screen result is positive. HBV DNA will be performed if the anti-HBc at visit 1 is positive and will be used for monitoring of these participants;
[c] Local urine testing will be standard unless serum testing is required by local regulation or IRB/IEC;
[d] Local requirements may apply; South Korea: see country/region-specific requirements (Appendix 11, Section 10.11).
Abbreviations: Ab = antibody; ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST =aspartate aminotransferase; anti-HBc = hepatitis B core antibody; HB = haemoglobin; HBsAg; Hepatitis B surface antigen; hCG = human chorionic gonadotropin; HDL = high density lipoprotein; Ig = immunoglobulin; LDL = low density lipoprotein; MCH = mean corpuscular haemoglobin; MCHC = mean corpuscular HB concentration; MCV = mean corpuscular volume; PCR = polymerase chain reaction; TSAT = transferrin saturation.

Description of laboratory supplies and procedures for obtaining, handling and transportation of samples will be available in the laboratory manual provided to sites. The investigator must keep an overview, e.g., a log, of laboratory samples not handled according to the laboratory manual. In addition, the investigator must keep an overview, e.g., a log, of laboratory samples stored at site.

All laboratory results will be reported to the sites on an ongoing basis, except laboratory results that could unblind the study which will not be reported to the sites until the study has been unblinded. These parameters include: hs-CRP, ziltivekimab concentration and anti-ziltivekimab antibodies. The investigator must review all laboratory results for concomitant illnesses and AEs. Local requirements may apply. Brazil: see country/region-specific requirements (Appendix 11, Section 10.11).

The central laboratory will communicate to the investigator abnormal values of parameters not requested in the protocol but identified by the laboratory equipment and/or their processes according to their laboratory SOPs. These data will not be transferred to the study database. The investigator should review such values for AEs and report these according to this protocol.

Laboratory samples analysed at the central laboratory and special laboratories (except PK samples stored for potential analysis of anti-ziltivekimab antibodies) will be destroyed no later than at finalisation of the CSR or as required according to local regulations (Appendix 11 (Section 10.11). For haematology samples (differential count) where the test result is not normal, then a part of the sample may be kept for up to two years or according to local regulations(Appendix 11 (Section 10.11). Human biosamples for retention (future research, analysis of anti-ziltivekimab antibodies as well as hypersensitivity reaction samples) will be stored as described in Appendix 7 (Section 10.7). Local requirements may apply. China: see country/region-specific requirements (Appendix 11, Section 10.11).

10.3 Appendix 3: Adverse Events and Serious Adverse Events: Definitions and procedures for recording, evaluating, follow-up, and reporting

10.3.1 Definition of AE

An AE is any untoward medical occurrence in a clinical study participant that is temporally associated with the use of IMP, whether or not considered related to the IMP. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease (new or exacerbated) temporally associated with the use of an IMP.

Events to be reported as AEs:

- Any abnormal laboratory test results or safety assessments considered clinically significant in the medical and scientific judgment of the investigator, including events that have worsened from prior to the time point from which AEs are collected.
- Conditions detected or diagnosed after IMP administration even though it may have been present prior to the time point from which AEs are collected.
- Exacerbation/worsening of a chronic or intermittent condition including either an increase in frequency and/or intensity of the condition.
- Signs, symptoms or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms or the clinical sequelae of a suspected overdose of IMP regardless of intent.
- A “lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition.

Events NOT to be reported as AE:

- Conditions present prior to the time point from which AEs are collected and anticipated day-to-day fluctuations of these conditions. This includes those conditions identified during screening or identified during other study procedures performed before exposure to IMP. Note: Conditions present or occurring prior to the time point from which AEs are collected should be recorded as concomitant illness/medical history.
- Medical or surgical procedures (e.g., endoscopy, appendectomy). The condition that leads to the procedure is the AE.
- Medical or surgical procedures not preceded by an AE or worsening of a known condition.

10.3.2 Definition of an SAE

An SAE is any untoward medical occurrence that fulfils at least one of the following criteria:

- **Results in death**
- **Is life-threatening**
    - The term ‘life-threatening’ refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death, if it were more severe.

- **Requires inpatient hospitalisation or prolongation of existing hospitalisation**
    - Hospitalisation signifies that the participant has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other seriousness criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious.
    - Hospitalisation for elective treatment (e.g., elective medical or surgical procedures) of a condition that was present prior to the time point from which AEs are collected, and that did not worsen, is not considered an AE. Note: Hospitalisations for administrative, study-related, social and convenience reasons do not constitute AEs and should therefore not be reported as AEs or SAEs. Hospital admissions for medical or surgical procedures, planned before study inclusion, are not considered AEs or SAEs.
- **Results in persistent or significant disability/incapacity**
    - The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experience of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g., sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- **Is a congenital anomaly/birth defect**
- **Important medical event:**
    - Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations. This includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious and reported as SAEs using the important medical event criterion.
    - The following must always be reported as SAEs using the important medical event criterion if no other seriousness criteria are applicable:
        - Suspicion of transmission of infectious agents via IMP.
        - Risk of liver injury defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3x UNL and total bilirubin >2x UNL where no alternative aetiology exists (Hy's law).

10.3.3 Description of adverse events requiring additional data collection and events for adjudication

An AE requiring additional data collection is an AE where Novo Nordisk has evaluated that additional data is needed in the evaluation of safety.

An AE requiring adjudication is an AE where Novo Nordisk has evaluated that adjudication is needed to confirm events in a consistent manner according to standardised criteria using independent external medical experts.

Description of AEs requiring additional data collection (on specific event form) and events for adjudication, are found in Table 8-1.

10.3.4 Recording and follow-up of AE and/or SAE

10.3.4.1 AE and SAE recording

The investigator will record all relevant AE/SAE information in the CRF.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event.

There may be instances when copies of source documents (e.g., medical records) for certain cases are requested by Novo Nordisk. In such cases, all participant identifiers, with the exception of the subject ID, must be redacted on the copies of the source documents before submission to Novo Nordisk (Section 10.1.5).

Please refer to Figure 10-1 for reporting timelines for non-serious AEs. For all non-serious AEs, the applicable forms should be signed when the event is resolved or at the end of the study at the latest. For sign-off of SAE related forms, refer to Section 10.3.5.

If an AE is considered to have a causal relationship with a concomitant medication, it is important that the suspected relationship is reported to Novo Nordisk, e.g., in the alternative aetiology section on the safety information form. Novo Nordisk may need to report this adverse event to relevant regulatory authorities.

10.3.4.2 Assessment of severity

The investigator will assess severity for each event reported during the study and assign it to one of the following categories:

- **Mild**: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- **Moderate**: A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- **Severe**: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. Note: An AE that is assessed as severe should not be confused with an SAE. Both AEs and SAEs can be assessed as severe.

10.3.4.3 Assessment of causality

The investigator is obligated to assess the relationship between IMP and the occurrence of each AE/SAE. The investigator will use clinical judgement to determine the relationship.

Relationship between an AE/SAE and the relevant IMP should be assessed as:

- **Probable** – Good reason and sufficient documentation to assume a causal relationship.
- **Possible** – A causal relationship is conceivable and cannot be dismissed.
- **Unlikely** – The event is most likely related to aetiology other than the IMP.

Alternative aetiology, such as underlying disease(s), concomitant medication, and other risk factors, as well as the temporal relationship of the event to IMP administration, will be considered and investigated.

The investigator should consult the ziltivekimab investigator's brochure[9] when making the causality assessment. For each AE/SAE, the investigator must document in the medical records that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report. However, **it is important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data.**

The investigator may change his/her opinion of causality, in light of follow-up information, and update the causality assessment in the CRF.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

10.3.4.4 Final outcome

The investigator will select the most appropriate outcome:

- **Recovered/resolved**: The participant has fully recovered, or by medical or surgical treatment the condition has returned to the level observed when first documented.
- **Recovering/resolving**: The condition is improving, and the participant is expected to recover from the event. This term may also be applicable for AEs ongoing at the time of death (where death was due to another AE). Note: For SAEs, this term is only applicable if the participant has completed the follow-up period and is expected to recover.
- **Recovered/resolved with sequelae**: The participant has recovered from the condition but with lasting effect due to a disease, injury, treatment or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE.
- **Not recovered/not resolved**: The condition of the participant has not improved, and the symptoms are unchanged, or the outcome is not known. Note, this term may be applicable in cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE).
- **Fatal**: This term is only applicable if the participant died from a condition related to the reported AE. Outcomes of other reported AEs in a participant before he/she died should be assessed as "recovered/resolved", "recovering/resolving", "recovered/resolved with sequelae" or "not recovered/not resolved". An AE with a fatal outcome must be reported as an SAE.
- **Unknown**: This term is only applicable if the participant is lost to follow-up.

10.3.4.5 Follow-up of adverse events and serious adverse events

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Novo Nordisk to elucidate the nature and/or causality of the AE or SAE as fully as possible (e.g., severe hypersensitivity reactions, Hy's law). This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognised follow-up period, the investigator should, upon request, provide Novo Nordisk with a copy of autopsy report including histopathology.

New or updated information should be recorded in the CRF. The investigator will submit any updated SAE data to Novo Nordisk without undue delay, but not later than within 24 hours of receipt of the information.

10.3.5 Reporting of serious adverse events

AE and SAE reporting via CRF

Relevant forms must be completed in the CRF.

For SAEs, initial notification via telephone is acceptable, although it does not replace the need for the investigator to complete the AE and safety information forms within the designated reporting timelines (as illustrated in Figure 10-1 below):

- AE form without undue delay, but not later than within 24 hours.
- Safety information form within 5 calendar days.
- Both the AE form and the safety information form must be signed within 7 calendar days after first knowledge by the investigator.
- The specific event form for AEs requiring additional data collection within 14 calendar days.
- For timelines related to events for adjudication; see Figure 10-1 and Appendix 8, Section 10.8.

If the eCRF is unavailable for more than 24 hours, then the site will use the paper AE form, and if the eCRF is unavailable for more than 5 calendar days, then the site will use the paper safety information form. The site should enter the SAE data into the eCRF as soon as it becomes available.

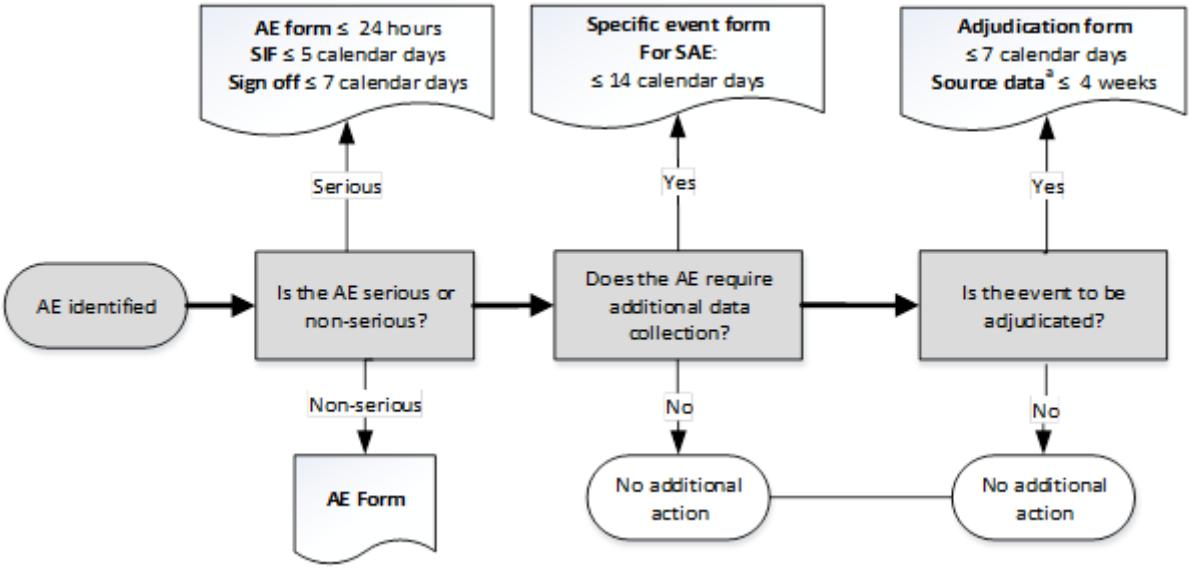
The relevant CRF forms (AE and safety information forms) must be forwarded to Novo Nordisk in accordance with Appendix 1, Section 10.1.5.

After the study is completed, the study database will be locked, and the eCRF will be decommissioned to prevent the entry of new data or changes to existing data. If a new SAE from a participant or updated information on a previously reported SAE needs to be reported after eCRF decommission, a paper AE and safety information form should be used to notify Novo Nordisk.

Contact details for SAE reporting can be found in the investigator trial master file.

Local requirements may apply. Germany: see country/region-specific requirements (Appendix 11, Section 10.11).

Figure 10-1 Decision tree for determining the event type and the respective forms to complete with associated timelines



Note: Timelines are from the awareness of an AE**. Queries and follow-up** request to be resolved ≤14 calendar days.
[a] If the EAS is not available for document upload, the investigator should ensure that the relevant source documents are collected and saved locally until EAS is available again;
In general data must be recorded in the CRF as soon as possible, preferably within 5 working days (Appendix 1, Section 10.1.8.1). For further information on events for adjudication, refer to Section 8.3 (Table 8-1) and Appendix 8 (Section 10.8).

Abbreviations: AE = adverse event; EAS = event adjudication system; SAE = serious adverse event; SIF = safety information form.

10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information

10.4.1 Definitions

Woman of childbearing potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanent sterile. If fertility is unclear (e.g., amenorrhea in adolescents or athletes), and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered. It must be recorded in the eCRF whether female participants are of childbearing potential.

Females in the following categories are not considered WOCBP:

1. Premenarcheal.
2. Females with one or more of the following:

- Documented hysterectomy.
- Documented bilateral salpingectomy.
- Documented bilateral oophorectomy.
- Females with permanent infertility due to an alternate medical cause other than the above (e.g., Müllerian agenesis, androgen insensitivity), investigator discretion should be applied in determining study enrolment.

3. Postmenopausal female:

- A postmenopausal state is defined as amenorrhoea for 12 months without an alternative medical cause in a female >45 year of age. Alternative medical causes for amenorrhoea include, but are not limited to, hormonal contraception or hormonal replacement therapy.
- Females ≥ 60 years of age can be considered postmenopausal.

Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt are considered of childbearing potential and will be required to use one of the highly effective contraception methods.

Note: Documentation regarding categories 1 to 3 can come from the site staff's review of participant's medical records, medical examination, or medical history interview.

10.4.2 Contraceptive guidance

Male participants

No contraception measures are required for male participants as the risk of teratogenicity/ fetotoxicity caused by transfer of ziltivekimab in seminal fluid is unlikely.

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use methods of contraception consistently and correctly.

Highly effective contraception is recommended to be utilised for at least 5 half-lives (285 days, ~10 months) after last dose of study intervention.

Table 10-3 lists the highly effective methods of contraception allowed. Local requirements may apply. Belgium, Brazil, Czech Republic, Denmark, Finland, Germany, Greece, Ireland, Italy, Latvia, Norway, Poland, Portugal, Romania, Spain, Thailand, UK: see country/region-specific requirements (Appendix 11, Section 10.11).

Table 10-3 Highly effective contraceptive methods allowed[68]

Highly effective methods[a] (Failure rate of <1% per year when used consistently and correctly):

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b,c]
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormone contraception associated with inhibition of ovulation[c]:
  - oral
  - injectable
  - implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)[b]
- Bilateral tubal occlusion
- Vasectomised partner
  Vasectomised partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential, and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.
- Sexual abstinence
  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 intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

Notes:

a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.
b) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines[68], acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.
c) It is recommended to add an additional acceptable contraception method (e.g., double barrier) for women on hormonal contraception as the effectiveness may be decreased with co-administration of ziltivekimab (Section 6.8.3).

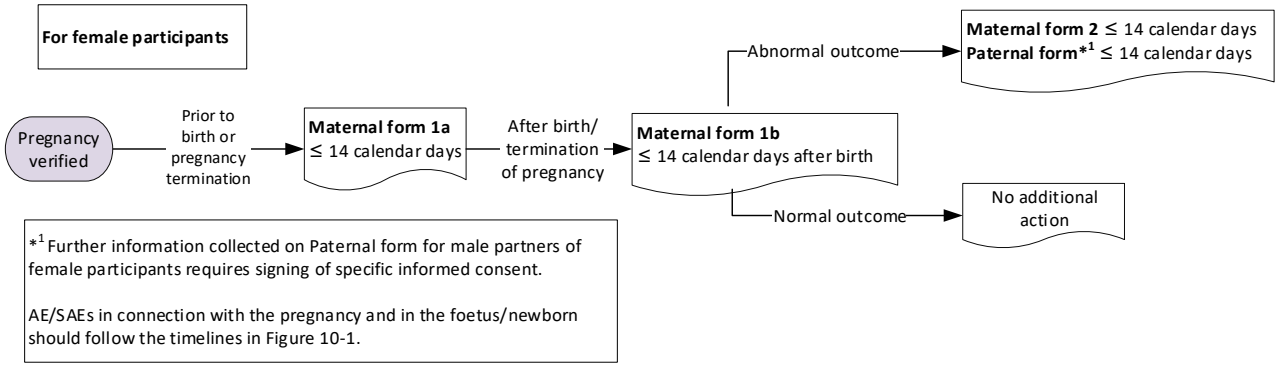
10.4.3 Collection of pregnancy information

Female participants who become pregnant

Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study.

Information will be recorded on the appropriate form and submitted to Novo Nordisk within 14 calendar days of learning of a participant's pregnancy (Figure 10-2).

Figure 10-2 Decision tree for determining the forms to complete for collection of pregnancy information and timelines for reporting – For female participants



The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on participant and neonate which will be forwarded to Novo Nordisk within 14 calendar days. Generally, follow-up will not be required for longer than 1 month beyond the delivery date.

Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for procedure.

While pregnancy itself is not considered to be an AE or SAE, any adverse event in connection with pregnancy or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. If relevant, consider adding ‘gestational’, ‘pregnancy-related’ or a similar term when reporting the AE/SAE.

Pregnancy outcome should be documented in the participant’s medical record. Abnormal pregnancy outcome (e.g., spontaneous abortion, foetal death, stillbirth, congenital anomalies and ectopic pregnancy) is considered an SAE. In case of abnormal pregnancy outcomes, paternal information should be recorded in the appropriate form after obtaining the necessary signed paternal informed consent (Appendix 1, Section 10.1.3).

If the investigator learns of an SAE occurring as a result of a post-study pregnancy which is considered related to the IMP by the investigator, the SAE should be reported to Novo Nordisk as described in Appendix 3, Section 10.3.

Any female participant who becomes pregnant while participating in the study must discontinue study intervention (Section 7.1.1). Furthermore, study intervention must be discontinued if the female participant is intent on becoming pregnant.

10.5 Appendix 5: Genetics

Genetic variation may impact a participant’s response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism and excretion, mechanism of action of the drug, disease aetiology, and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, blood samples will be collected for DNA/RNA/epigenetic analysis from consenting participants.

Blood samples for DNA, RNA or epigenetic analysis will be collected from participants who have consented to participate in the optional biobank component of the study (Section 8.7). Refer to Appendix 7 (Section 10.7) for further details regarding retention of human biosamples. Local requirements may apply. Brazil, China, Colombia, Finland, Israel, South Africa, South Korea: see country/region-specific requirements (Appendix 11, Section 10.11).

The specimens collected for optional genomic research will be used to identify or validate genetic markers that may increase our knowledge and understanding of ziltivekimab and of the biology of inflammatory, cardiometabolic, kidney and other related diseases and to study the association of genetic markers with disease pathogenesis, progression and/or treatment outcomes, including efficacy, AEs, and the processes of drug absorption and disposition. These specimens may be used also to develop biomarker or diagnostic assays and establish the performance characteristics of these assays. The collection and analysis of optional genomic specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualised drug therapy for participants in the future. Additional analyses may be conducted if it is hypothesised that this may help further understand the clinical data.

The samples may be analysed as part of a multi-study assessment of genetic factors involved in the response to ziltivekimab or product treatments of this class to understand the studied disease or related conditions.

The results of genetic analyses will be reported in a separate study report.

Novo Nordisk will store the DNA/RNA/epigenetic samples in a secure storage space with adequate measures to protect confidentiality, as described in Appendix 7 (Section 10.7).The samples will be retained while research study intervention of this class or indication continues, but no longer than 15 years.

10.6 Appendix 6: Technical complaints: Definition and procedures for recording, evaluation, follow-up and reporting

10.6.1 Definition of technical complaint

A technical complaint is any written, electronic or oral communication that alleges product (medicine or device) defects. The technical complaint may be associated with an AE but does not concern the AE itself.

Examples of technical complaints:

- Problems with the physical or chemical appearance of study interventions (e.g., discoloration, particles or contamination).
- Problems with packaging material including labelling.
- Problems related to the prefilled syringe (e.g., to the injection mechanism or the needle).

Time period for detecting technical complaints

All technical complaints which occur from the time of receipt of the product at site until the time of the last usage of the product must be collected for products predefined on the technical complaint form.

10.6.2 Recording and follow-up of technical complaints

Reporting of technical complaints to Novo Nordisk

For contact details for Customer Complaint Center, please refer to Attachment I.

Technical complaints on products allocated to a participant must be reported on a separate technical complaint form:

One technical complaint form must be completed for each affected dispensing unit number (DUN).

Timelines for reporting of technical complaints to Novo Nordisk

The investigator must complete the technical complaint form in the eCRF within the following timelines of obtaining knowledge of the technical complaint:

- 24 hours if related to an SAE.
- 5 days calendar for all other technical complaints.

If the eCRF is unavailable, make sure the related SAEs are reported via paper forms within 24 hours. When the eCRF becomes available again, the investigator must enter the information on the technical complaint form in the eCRF. In order to report a technical complaint on a study intervention listed on the technical complaint form but not allocated to a participant, use the paper technical complaint form.

Follow-up of technical complaints

The investigator is responsible for ensuring that new or updated information will be recorded on the originally completed form.

Collection, storage and shipment of technical complaint samples

The investigator must collect the technical complaint sample and all associated parts and notify the monitor within 5 calendar days of obtaining the sample at site. The sample and all associated parts must be sent as soon as possible to Customer Complaint Center, Novo Nordisk, together with a copy of the completed technical complaint form. The technical complaint sample should contain the batch, code or lot number and, if available, the DUN. If the technical complaint sample is unobtainable, the reason must be stated on the technical complaint form. If several samples are shipped in one shipment, the sample and the corresponding technical complaint form should be kept together.

Storage of the technical complaint sample must be done in accordance with the conditions prescribed for the product.

10.7 Appendix 7: Retention of human biosamples for future research

Local requirements may apply. Brazil, China, Colombia, Finland, Israel, South Africa, South Korea: see country/region-specific requirements (Appendix 11, Section 10.11).

10.7.1 Biosamples for future research

Study participants who do not wish to contribute with biosamples for storage may still participate in the study. Participants must sign and date a separate informed consent form before biosamples are collected to be stored for future analysis.

In countries where allowed, and in participants providing informed consent, the study will involve collection of human biosamples to be stored in a central archive for future use as noted in Sections 8.7 and 8.8.

The following samples will be stored:

- Whole blood (for genetic or epigenetic analyses).
- EDTA plasma and serum (for future analyses of circulating biomarkers).

The samples need to be frozen and should be sent in batches to the central laboratory. The biosamples will be stored at a secure central bio-repository after end of study and until marketing authorisation approval or until the research project terminates, but no longer than 15 years from end of study after which they will be destroyed. The biosamples may be transferred to other countries for analysis, if not prohibited by local regulations, and will be destroyed at the latest 15 years after end of study. Only relevant Novo Nordisk staff and consultants, auditors, research organisations or laboratories working for Novo Nordisk and biorepository personnel will have access to the stored samples and associated data.

The participant may request the stored biosamples for future research to be destroyed by withdrawing the designated informed consent at any timepoint during and after the study. For samples that have already been analysed, the results can still be used for scientific research and will not be removed from the datafile.

The participant's identity will remain confidential, and the samples will be identified only by subject ID, visit number and study identification number. No direct identification of the participant will be stored together with the samples. Confidentiality and personal data protection will be ensured during storage after the end of study. In the event that the collected biosamples will be used in the future, care will be taken to target analyses within the scope defined in Sections 8.7 and 8.8.

The analyses are likely to be performed after the study has come to an end, and results will therefore not be part of the CSR.

10.7.2 Anti-ziltivekimab-antibodies samples

Anti-ziltivekimab-antibodies samples will not be obtained in this study. The PK samples (Section 8.4) will be stored and used for anti-drug antibody analysis in case of suspected hypersensitivity reaction, if relevant for overall PK/PD assessment or if requested by Health Authorities.

Remaining and residual antibody samples (Sections 8.4 and 8.6) already collected may be retained after end of study.

- The samples will be stored at Novo Nordisk or a biorepository assigned by Novo Nordisk after end of study and until marketing authorisation approval or until the research project terminates, but no longer than 15 years from the end of study after which they will be destroyed.
- Only relevant Novo Nordisk staff and consultants, auditors, research organisations or laboratories working for Novo Nordisk and biorepository personnel will have access to the stored samples and associated data.
- The samples may be transferred to other countries for analysis, if not prohibited by local regulations, and will be destroyed at the latest 15 years after end of study.
- The identity of study participants will remain confidential, and the samples will be identified only by subject ID, visit number and study identification number. No direct identification of the participant will be stored together with the samples.

The retained samples may be used to:

- Evaluate safety or efficacy aspects that address concerns arising during or after the study.
- Further characterise the antibody responses towards the drug, if required by health authorities or for safety reasons.
- Conduct further analytical method development and validation of antibody assays.
- Genetic analyses will not be performed on these samples.

10.7.3 Hypersensitivity reaction samples

In order to comply with any future requests from health authorities to further characterise the antibody response, antibody samples collected in relation to suspicion of a severe systemic hypersensitivity reaction[53] (Section 8.6.1) may be retained.

The samples will be stored at Novo Nordisk or a Novo Nordisk designated referral central bio-repository. The samples might be transferred to other countries, if not prohibited by local regulations. Only Novo Nordisk staff and bio-repository personnel will have access to the stored samples. The samples may be shipped to a contract research organisation (CRO) for analysis.

The samples will be pseudonymised (identified only by subject ID, visit number, study identification number and sampling date). Confidentiality and personal data protection will be ensured during storage after the end of study and no direct identification of the participant will be stored together with the samples.

Potential further analyses of the samples will not have any consequences for the participant and their relatives. Participants can contact the investigator if they wish to be informed about results derived from stored antibody samples obtained from their own body.

The samples will be stored after end of study and until marketing authorisation approval or until the research project terminates, but no longer than 15 years from end of study after which they will be destroyed. PK study samples will be destroyed (upon approval by Novo Nordisk) after marketing authorisation approval.

10.8 Appendix 8: Events requiring adjudication

The list of events for adjudication can be found in Table 8-1 and the reporting timelines in Figure 10-1.

Event adjudication will be performed in randomised participants. These events are reviewed by an independent external EAC in a blinded manner; refer to Section 8.3 for further details.

There are four ways to identify events relevant for adjudication as described below:

1) Investigator-reported events for adjudication: investigator selects the appropriate AE category relevant for adjudication (Table 8-1).
2) AEs with fatal outcome.
3) AE search (standardised screening): All AEs not reported with an AE category relevant for adjudication will undergo screening to identify potential events for adjudication. Investigators will be notified of these events in the eCRF.
4) EAC-identified events: Unreported events relevant for adjudication identified by the EAC during review of source documents provided for another event for adjudication. Investigators will be notified of these events in the eCRF and has the option to report the EAC-identified event.

For each event relevant for adjudication an event type specific adjudication form should be completed in the eCRF within 7 days (Figure 10-1). Copies of source documents should be uploaded to the event adjudication system (EAS) as soon as possible and preferably within 4 weeks (Figure 10-1). In cases where the EAS is not accessible for document upload, the investigator should ensure that the relevant source documents are collected and saved locally until the EAS is available. If no, or insufficient source documents are provided to the adjudication supplier, the investigator can be asked to complete a clinical narrative to be uploaded to the EAS.

If new information becomes available for an event sent for adjudication, it is the responsibility of the investigator to ensure the new information is uploaded to the EAS.

An Event Adjudication Site Manual will be provided to each site detailing which source documents are relevant and how these should be provided to the adjudication supplier. The anonymisation and labelling requirements are also described in the site manual.

10.9 Appendix 9: Vaccines

The general guidance with regard to patients who are immunocompromised is that the immunogenicity of the vaccine (host's immune response to the vaccine) might be impaired by the use of ziltivekimab (or other immunosuppressive agents).

Because of the broad range of vaccine approaches being taken in different countries, the current study aims to accommodate local guidance for COVID-19 vaccination and other vaccines for study participants. Note that only approved vaccines including COVID-19 vaccines are allowed, and that co-participation (i.e., signed informed consent) in any other interventional clinical study of an approved or non-approved investigational medicinal product including vaccines is not permitted during the study.

A general guidance regarding allowed and not-allowed vaccines are provided below, including examples of vaccine types and specific vaccines. Note that the examples provided reflects the current knowledge and status at time of finalisation of this document.

10.9.1 Vaccines in general

10.9.1.1 Allowed vaccines

All approved not-live and not attenuated-live vaccines can be administered safely to participants with altered immunocompetence[69], whether the vaccine is a killed whole-organism or a subunit, split-virus, toxoid, polysaccharide, or polysaccharide protein-conjugate vaccine; examples of diseases with this vaccine type are provided in Table 10-4.

Table 10-4 Allowed vaccines

Type of vaccine	Examples	Disease
Not-live and not attenuated-live vaccines	Diseases that have known not-live and not attenuated-live vaccines	• Hepatitis A • Flu • Polio • Rabies
	Diseases that have subunit, recombinant, polysaccharide, and conjugate vaccines	• Hib (Haemophilus influenzae type b) disease • Hepatitis B • HPV (Human papillomavirus) • Whooping cough (part of the DTaP combined vaccine) • Pneumococcal disease • Meningococcal disease • Shingles[a]
	Toxoid vaccines	• Diphtheria Tetanus

[a] Note that live shingles vaccines are also available, but not allowed.

10.9.1.2 Non allowed vaccines

Live or attenuated-live vaccines must not be administered concomitant with study intervention; examples of diseases with this vaccine type are provided in Table 10-5.

Table 10-5 Not allowed vaccines

Type of vaccine	Examples	Disease
Live or attenuated-live vaccines	Diseases that have known live-attenuated vaccines	• MMR • Varicella • MMRV • LAIV • Yellow fever • Ty21a oral typhoid • BCG • Smallpox • Rotavirus

10.9.2 COVID-19 vaccines

Because of the potential serious sequalae of a COVID-19 infection and the broad range of vaccine approaches being taken in different countries, the study protocol aims to accommodate the use of COVID-19 (and other) vaccines according to local guidelines.

The only contraindicated vaccines for study participants are live or attenuated-live vaccines because of the general guidance about use of these vaccines in immunocompromised patients and as IL-6 inhibition may impact the magnitude of an immune response to new antigens.

Below is an overview of not-live and not attenuated-live vaccines under development and not-live and not attenuated-live vaccines currently approved[70] that will be allowed in the study if approved by local authorities.

10.9.2.1 Allowed COVID-19 vaccine types (when approved by local authorities)

Concomitant therapy with not-live and not attenuated-live COVID-19 vaccine types are allowed in the study, provided that the vaccine has been approved by local authorities. Not-live and not attenuated-live COVID-19 vaccines include vaccines based on SARS-CoV-2 proteins, naked DNA-based vaccines, mRNA-based vaccines and vaccines based on viral vectors; examples of these vaccine types are provided in Table 10-6. An updated list of approved not-live and not attenuated-live COVID-19 vaccine is available at the WHO website: https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines.

Table 10-6 Allowed COVID-19 vaccine types (when approved by local authorities)

Type of vaccine	Examples	Sponsor
Vaccines based on SARS-CoV-2 proteins	Spike protein or its fragments plus adjuvant vaccines	Adimmune, Taiwan Bektop, Russia Biotechnology Vector, Russia Clover Biopharmarm plus GSK adjuvant, China-Italy CoVaxx, US Inst Finlay de Vacuna Vaccine, Cuba plus adjuvant Medigen, Taiwan-US, plus CpG adjuvant Sanofi plus GSK adjuvant, France – Italy

Type of vaccine	Examples	Sponsor
		The Univ of Queensland, Australia
		Univ Tübingen, Germany
		Vaxine, Australia, plus adjuvant
		West China Hosp Sichuan Univ., China
		ZFSW Anhui Zhifei Longcom, China, plus adjuvant
	Proteins carried by nanoparticles vaccines	Novavax, US
		US, Australia, and South Africa, plus adjuvant
	Oral tablet containing spike protein fragments vaccine	Vaxart, US
	Microneedle skin patch delivering Spike proteins vaccines	Univ Queensland, Australia
	Spike protein or its fragments inserted in virus-like particles (VLP) vaccines	SpyBiotech/Serum Institute of India, India
	Tobacco plant-produced proteins vaccines	Kentucky Bio Processing, US
	Tobacco plant-produced proteins in virus like particles (VLP) vaccines	Medicago plus GSK adjuvant, US – Italy
Naked DNA-based vaccines	Naked DNA plasmids vaccines	Zydus Cadila, India
		AnGes, Japan; Takis, Italy
	Naked DNA plasmids plus electroporation vaccines	Inovio, US
		Genexine, Korea
		Karolinska Inst, Sweden
		Inovio, Italy
mRNA-based vaccines	Lipid vesicles (Liposomes) mRNA vaccine	Abogn, China
		CureVac, Germany
		Moderna, US
		Pfizer, US - BioNTech, UK
	Nanoparticles mRNA vaccine	Arcturus Ther, Singapore
Vaccines based on viral vectors	Engineered non-replicating virus vectors	Chimpanzee adenovirus: AstraZeneca, Univ. Oxford, Sweden-UK-Italy
		Gorilla adenovirus: ReiThera, Italy
		Human adenovirus: CanSino, China
		Johnson&Jonhson; Acad Mil Med Sci, China; Gamaleya Res Inst, Russia

10.9.2.2 Non allowed COVID-19 vaccines

Live or attenuated-live COVID-19 vaccines must not be administered concomitant with study intervention; examples of this vaccine type are provided in Table 10-7.

Table 10-7 Non allowed COVID-19 vaccines

Type of vaccine	Examples	Sponsor/institution
Live or attenuated-live vaccines	Attenuated SARS-CoV-2 vaccines (currently in nonclinical development phase)	The Serum Inst of India, India, in collaboration with Codagenix, a New York private biotech.
		Indian Immunologicals Ltd, India, in collaboration with the Griffith University, Australia.
		Mehmet Ali Aydunar Univ, Turkey.

10.10 Appendix 10: Mitigations to ensure participant safety and data integrity during an emergency situation

A major emergency is defined as a situation that causes substantial restrictions to study site access for participants and/or sponsor representatives, e.g., pandemics (COVID-19) or natural disasters such as hurricanes, floods and large-scale fires.

In case local restrictions lead to lockdown of a site or pharmacy or a restriction of movement of participants, the site must contact Novo Nordisk to allow for implementation of the mitigations mentioned in this appendix based on mutual agreement. Implementation of specific mitigations should be based on assessment of feasibility at the individual site.

Sites should comply with local regulations, requirements and/or guidelines if they have been issued. According to local regulation, health authorities and independent ethics committees should be notified in case elements of the emergency appendix are activated.

10.10.1 Visits

Key visits (Section 8) should be performed as physical on-site visits, if in any way possible. If not, assessments can be conducted remotely using telemedicine (video, phone or similar) or as home visits.

Visits during the screening period (visit 1) and randomisation (visit 2) should always be performed as physical on-site visits. If a site is unable to perform these visits on-site, screening and randomisation of new participants at that site should be on hold until on-site visits are possible.

In case local restrictions lead to the lockdown of a site or pharmacy or a restriction of movement of participants, site visits can be performed as home nursing by the site staff. Local requirements may apply. Bulgaria, Czech Republic: see country/region-specific requirements (Appendix 11, Section 10.11).

On-site visits are always preferred, but study assessments can be performed by site staff visiting the participant´s home/residence/location (or at alternative location) if needed. As a prerequisite it must be ensured that study site staff is covered by workers' compensation insurance to protect workers. The preferred order for the method of assessment is: on-site, home visit by the site staff, video, phone.

At each visit, the investigator must indicate in the eCRF how the visit was performed and specify the reason for the preferred assessment method.

10.10.2 Assessments

Sites should always try to follow the assessments outlined in the flowchart (Section 1.2) to the extent possible. Implementation of specific mitigations should be based on assessment of feasibility at the individual site.

Assessments used for evaluation of participants safety or the confirmatory endpoints should be prioritised.

Local laboratories or diagnostic facilities can be used for critical safety laboratory assessments at the investigator's discretion if on-site visits are not possible or e.g., in case of temporary lockdown of the central laboratory. Abnormal clinically relevant findings should be reported in the eCRF as AEs, if fulfilling the criteria (Appendix 3, Section 10.3). Special attention should be made to the AEs that feed into primary and confirmatory secondary endpoints.

For all assessments done at the participant´s home/residence/location, site specific equipment has to be used and procedures in the laboratory manual have to be followed. It must be documented in the medical records that the participant has consented to this process, and if any local requirements for informed consent applies, these must be followed.

Home measurements of weight and vital signs can be performed if on-site visits are not possible and if deemed feasible for the participant. Only findings meeting the definition for an AE (refer to Appendix 3, Section 10.3) should be reported in the eCRF.

If the assessments indicated for key visits (Section 8) in the flowchart (Section 1.2) cannot be performed as on-site visits, using telemedicine or be analysed at a local laboratory or diagnostic facility, they should be performed at the first possible time point following the originally scheduled visit in agreement with Novo Nordisk.

10.10.3 Study intervention

Study intervention alternative dispensing methods

For selected countries and if permitted by local regulations alternative dispensing methods of study intervention may be implemented, and details will be communicated and documented. The dispensing options will be provided by Novo Nordisk A/S and will be based on options and requirements at country/region level and if permitted by local regulations.

If participants are not able to attend visits 3 and 5 at the study site, training in handling and self-administration of study intervention may be performed remotely.

10.11 Appendix 11: Country/region-specific requirements

10.11.1 Argentina

- Sections 1.2 and 5.2, Exclusion criterion #25: A serology test for HIV will be performed to every patient in screening that does not have a recent HIV serology prior to the screening visit. A patient's previous HIV serology test should be considered recent if the test was performed within the last year prior to the date of the screening visit. Even if the patient has a previous recent HIV test, a new test may be performed at the discretion of the investigator.
- Sections 1.2 (Flowchart), 8.2.9 (Pregnancy testing) and 5.2, Exclusion criterion #3: Contraceptive measures considered adequate include highly effective contraceptive methods in accordance with the CTFG (Clinical Trial Facilitation Group) "Recommendations related to contraception and pregnancy testing in clinical trials".[68] This means that the use of double barrier methods is not applicable for Argentina. Monthly testing with highly sensitive urine pregnancy tests is required for woman of childbearing potential. The contraceptive methods and pregnancy tests will be reimbursed by the sponsor.
- Sections 5.2 (exclusion criterion #26) and 8.2.7 (tuberculosis screening): All participants in Argentina must undergo testing for latent TB with a central lab QuantiFERON-TB test unless the participant has a QuantiFERON-TB test or T-SPOT.TB test no more than 90 days old at screening (visit 1), documented in medical records.
- Section 6.6, Continued access to study intervention after end of study: Participants requiring to continue their treatment after the study completion shall have access to the intervention that turned out to be beneficial or to an alternative intervention or another proper benefit, which shall be approved by the Ethics Committee for the time it decides or until such access is ensured by any other means.

10.11.2 Australia

- Appendix 1 (Section 10.1.13): Comply with Medicines Australia Guidelines for Compensation for Injury Resulting from Participation in a Company Sponsored Clinical Trial, version 160104 16 January 2004.

10.11.3 Austria

- Sections 5.2 (Exclusion criterion #3) and 8.2.9 (Pregnancy testing): Use of double contraceptive method is required for WOCBP. A monthly pregnancy test is mandatory for female subjects of childbearing potential.
- Appendix 1 (Section 10.1.13): Arzneimittelgesetz (BGBI. I Nr. 8/2022) last amended with BGBl. I Nr. 59/2018.

10.11.4 Belgium

- Section 5.2 (exclusion criterion #3) and Appendix 4 (Section 10.4.2: Contraceptive measures considered adequate include highly effective contraceptive methods in accordance with the CTFG (Clinical Trial Facilitation Group): Recommendations related to contraception and pregnancy testing in clinical studies.[68] Hence, highly effective methods of birth control are defined as those, alone or in combination, that result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly, such as implants, injectable, combined oral

contraceptive, some IUDs, true sexual abstinence (i.e. refraining from heterosexual intercourse during the entire period of risk associated with the study intervention) or vasectomised partner. This means use of double barrier methods is not applicable for Belgium.

- Section 6.6: Participants may receive post-study access to the investigational product if:
  - the benefit/risk ratio is favourable for the participants and no satisfactory treatment is available on the market in Belgium,
  - the competent Belgian health authorities approve this access, and
  - the development and manufacturing of the IMP is continued.
- Appendix 1 (Section 10.1.13), Indemnity statement: Novo Nordisk accepts liability in accordance with: Law concerning experiments on the human person of 07 May 2004 – Article 29: §1. Even if without fault, Novo Nordisk is liable for the damage which the participant and/or his rightful claimants sustain, and which shows either a direct or an indirect connection with the study.

10.11.5 Bosnia

No country-specific requirements apply.

10.11.6 Brazil

- Section 5.2, Exclusion criterion #3: According to resolution 466/12 use of contraceptive methods are not mandatory for women who declare freely no risk of pregnancy, either by not engaging in sexual activity or by having sexual activity with no birth potential risk.
- Section 5.2, Exclusion criterion #4: Participation in other studies within 1 year prior to screening visit (visit 1), unless there is a direct benefit to the research participant at the investigator's discretion (according to Resolution 251/97, item III.2.j).
- Section 6.4.3, Adherence to standard of care: Novo Nordisk will reimburse costs of standard-of-care treatment.
- Section 6.6: At the end of the study, all participants should be assured the access to the best proved prophylactic, diagnostic and therapeutic methods identified during the study, in accordance with resolution CNS 466/12.
- Sections 8.7 and 8.8, Appendix 5 (Section 10.5) and Appendix 7 (Section 10.7): No participants from Brazil will take part in the optional biobank component of the study where collected samples will be used for future research and genotype tests.
- Sections 8.7 and 8.8 and Appendix 7 (Section 10.7): According to Brazilian resolution, retention of human bio-specimens must follow specific resolution Res. CNS 441/11. Biological samples from Brazil will be destroyed at the end of the study.
- Appendix 1 (Section 10.1.3): Two original informed consent forms will be signed and dated and one original will be given to the participant (according to resolution CNS 466/12).
- Appendix 1 (Section 10.1.13), Indemnity statement: Novo Nordisk takes responsibility for their products and the responsibilities set out in legislation, laws and/or special rules for the conduct of research studies in Brazil. If the study participant has questions or believes to have suffered any medical harm as a result of their participation in this research, the study team should be contacted immediately. If the study participant suffers any harm directly or indirectly, now or later caused by the study procedures (which the study participant would not have been exposed to if not participating in the study) or the administration of study medication, Novo Nordisk will ensure that the study participant will receive full care for such harm at no cost for as long as

necessary. If any harm occurs as described above, the study participant is entitled to receive compensation in accordance with applicable Brazilian law.

- Appendix 2 (Section 10.2): All laboratory results will be communicated to the investigators.
- Appendix 4 (Section 10.4.2), Contraception: Contraceptive measures considered adequate include highly effective contraceptive methods in accordance with the CTFG (Clinical Trial Facilitation Group) "Recommendations related to contraception and pregnancy testing in clinical trials".[68] This means that the use of double barrier methods is not applicable for Brazil.

10.11.7 Bulgaria

- Appendix 1 (Section 10.1): According to Regulation 31 (for defining the rules of Good Clinical Practice, 12 Aug 2007), art. 4, par. (2) - The protocol is prepared according to the requirements of GCP and contains as a minimum the following:
  1) assessment of the expected benefits and risks;
  2) definition of inclusion and exclusion criteria;
  3) rationale for study population, especially when it is expected to include patients that cannot consent personally and other vulnerable groups;
  4) description of the procedures for recruiting patients and getting informed consent when it is expected to include patients who are temporarily or constantly unable to consent personally and when it is expected to receive consent from an independent witness;
  5) description of the plan and the procedures for assuring complementary medical cares for the participants after the study is ended;
  6) monitoring procedures;
  7) publication policy.
- Section 10.10.1: Home visits are not applicable to Bulgaria.

10.11.8 Canada

No country-specific requirements apply.

10.11.9 China

- Section 3.1: Exploratory objectives and endpoints are not applicable for participants from China.
- Section 4.1, Overall design: The recruitment period in China may be extended beyond 36 months from global FPFV due to the relative longer study initiation timeline and participant recruitment challenges.
- Sections 5.1, 5.2 and 5.6: The criteria will be assessed at the investigator's discretion unless otherwise stated.
- Sections 8.1.1, 8.2.4, 8.7 and 8.8 and Appendix 2 (Section 10.2): The samples tested at sites will be destroyed as biological waste according to local regulation, if applicable. Samples for Chinese participants will not be tested outside China. The samples tested at the central lab will be destroyed as biological waste according to local regulation and lab manual. The laboratory samples for Chinese participants will be destroyed according to local regulatory requirement. No sample will be stored after the latest date of local regulatory approval.
- Section 8.7 and 8.8, Appendix 5 (Section 10.5) and Appendix 7 (Section 10.7): No participants from China will participate in the optional biobank part of the study, and no genetic testing will be performed.

- Appendix 1 (Section 10.1), Regulatory, ethical, and study oversight considerations:
- Any study procedure conducted in China mainland should comply with "Regulations on management of Human Genetic Resources of People's Republic of China" and relative guideline. http://www.gov.cn/zhengce/content/2019-06/10/content_5398829.htm.
- Regulatory authorities will receive the clinical trial application, protocol amendments, reports on SAEs, and the CTR according to national requirements.
- For China, an international cooperative relevant report of related China's Human Genetic Resources will be submitted based on local regulation.
- Appendix 1 (Section 10.1.7): Information of the study will be disclosed at clinicaltrials.gov, chinadrugtrials.org.cn and novonordisk-trials.com as China HA has requested to disclose study information (phase 1-3) at chinadrugtrials.org.cn since 2013.
- Appendix 1 (Section 10.1.10), Retention of clinical study documentation: About site specific data storage, sites have the equal right with Novo Nordisk. Long term preservation of Chinese Patients' Trial Data is Prohibited in any other entities.
- Appendix 7 (Section 10.7), Retention of human biosamples for future research: If required by health authorities, antibody samples, biomarker samples, and other special test samples will be retained for further analysis and/or characterisation of responses towards drug. These samples (include their backup) will be stored at a central bio-repository after end of study and until marketing authorisation approval or until the research project terminates, after which they will be destroyed. All samples' collection, shipment, analysis, temporary storage and destruction will be clearly recorded. The subjects' identity will remain confidential and the samples will be identified only by subject number, visit number and study identification number. No direct identification of the subject will be stored together with the samples. Only Novo Nordisk staff and laboratory personnel involved in the analyses will have access to the stored antibody samples. Subjects can contact the investigator if they wish to be informed about results derived from stored antibody samples obtained from their own body.

10.11.10 Colombia

- Sections 8.7 and 8.8, Appendix 5 (Section 10.5) and Appendix 7 (Section 10.7): No participants from Colombia participate in the optional biobank part of the study where collected samples will be used for future research, and no genetic testing will be performed.

10.11.11 Croatia

No country-specific requirements apply.

10.11.12 Czech Republic

- Sections 1.2, 5.1 and 8.9: Date of birth: participant's full date of birth is not allowed to be collected and must be shortened to year of birth.
- Sections 1.2 and 8.2.9: Monthly testing with highly sensitive urine pregnancy tests are required for WOCBP.
- Section 4.4.1: End of study assessments. Section describes the option of using a search agency to facilitate identifying updated contact details for a missing participant or provide vital status (dead or last alive date). Providing patient's personal data to a third party for the purposes of a clinical study is not permitted in the Czech Republic.

- Section 5.2, exclusion criterion #3 and Appendix 4 (Section 10.4.2): Contraceptive measures considered adequate include highly effective contraceptive methods in accordance with the CTFG (Clinical Trial Facilitation Group): Recommendations related to contraception and pregnancy testing in clinical studies.[68] This means use of double barrier methods is not applicable for Czech Republic.
- Sections 5.2 (exclusion criterion #26), and 8.2.7: All participants must undergo testing for latent TB with a central lab QuantiFERON-TB test unless the participant has a QuantiFERON-TB or T-SPOT.TB test no more than 90 days old at screening (visit 1), documented in medical records.
- Sections 6.2.1 (Study intervention administration and dispensing) and 6.2.5 (Shipment of study intervention to participant's home/residence/location). These sections provide the option of providing study intervention from the study site or pharmacy to the participant's home/residence/location by courier service. This possibility is only allowed in the Czech Republic if the circumstances are extraordinary, such as during a pandemics.
- Appendix 10 (Section 10.10): Mitigations to ensure participant safety and data integrity during an emergency situation. The appendix includes the possibility of home health visits. If this possibility of home care is used in the Czech Republic, the guideline issued by the State Institute for Drug Control on 13 May 2020 must be complied with: https://www.sukl.cz/leciva/home-care?highlightWords=home+care

10.11.13 Denmark

- Section 5.2, exclusion criterion #3 and Appendix 4 (Section 10.4.2: Contraceptive measures considered adequate include highly effective contraceptive methods in accordance with the CTFG (Clinical Trial Facilitation Group): Recommendations related to contraception and pregnancy testing in clinical studies.[68] This means use of double barrier methods is not applicable for Denmark.
- Appendix 1 (Section 10.1.5), Data protection: The participant must be informed about his/her privacy rights, including that his/her personal study-related data will be used by Novo Nordisk in accordance with local data protection law in the given country of data handling.

10.11.14 Estonia

No country-specific requirements apply.

10.11.15 Finland

- Section 5.2, exclusion criterion #3 and Appendix 4 (Section 10.4.2): Contraceptive measures considered adequate include highly effective contraceptive methods in accordance with the CTFG (Clinical Trial Facilitation Group): Recommendations related to contraception and pregnancy testing in clinical studies.[68] This means use of double barrier methods is not applicable for Finland.
- Sections 8.7 and 8.8, Appendix 5 (Section 10.5) and Appendix 7 (Section 10.7): No participants from Finland will participate in the optional biobank part of the study where collected samples will be used for future research, and no genetic testing will be performed.

10.11.16 France

- Sections 1.2, 5.1 and 8.9: Date of birth: participant's full date of birth is not allowed to be collected and must be shortened to year of birth.
- Section 4.4.1 and 7.3: It is not permitted to obtain health information from publicly available sources in France.
- Section 5.2 (exclusion criterion #6): According to French regulation (CSP art 1121 5, 7 and 12), incapacitated patients, protected minors and patients in emergency situation are not eligible for participation in clinical studies in France.
- Section 6.6: If at the end of the study the participant has a beneficial effect from the study medicine, the investigator may, in agreement with the sponsor, decide to continue the treatment through an ATU request (temporary authorisation for use) before the study medication is potentially marketed.
- Section 8.9: Race and ethnicity are not allowed to be collected by local regulation.
- Appendix 1 (Section 10.1.13), Indemnity statement: According to the French Public Health Code article L.1121-10 (law n° 2004-806 of 9 August 2004 art. 88 I, IX Journal Officiel of 11 August 2004, 'The sponsor is responsible for identification of the harmful consequences of the biomedical research for the person lending himself thereto and for indemnification of his beneficiaries, except in case of proof, incumbent on it, that the prejudice is not attributable to his fault of or the fault of any intervening party, without the sponsor's being entitled to call on acts by a third party or the voluntary withdrawal of the person who had initially consented to cooperating in the research'.

10.11.17 Germany

- Sections 1.2, 5.1 and 8.9: Date of birth: participant's full date of birth is not allowed to be collected and must be shortened to year of birth.
- Sections 1.2 and 8.2.9: Monthly testing with highly sensitive urine pregnancy tests are required for WOCBP.
- Section 5.1 (inclusion criteria #3 and 4): Patients from Germany participating in the prevalence study (NN6018-7527) may be enrolled based on the hs-CRP and/or NT-proBNP (requiring corresponding ECG from the same date) results obtained in the study, if no more than 30 days old.
- Section 5.2 (exclusion criterion #27): Patients from Germany participating in the prevalence study (NN6018-7527) may be enrolled based on the eGFR results obtained in the study, if no more than 30 days old.
- Sections 5.2 (exclusion criterion #26), and 8.2.7: Laboratory results of tuberculosis test results can be no more than 30 days old at screening.
- Appendix 3, Section 10.3.5, Reporting of serious adverse events:
  - All AEs, irrespective of seriousness, should be collected from the day of randomisation and until the follow-up visit/end of study visit, at the time points specified in the flowchart.
  - All SAEs must be reported to Novo Nordisk immediately without undue delay.
- Appendix 4 (Section 10.4.2): Contraceptive measures considered adequate include highly effective contraceptive methods in accordance with the CTFG (Clinical Trial Facilitation Group): Recommendations related to contraception and pregnancy testing in clinical studies.[68] This means use of double barrier methods is not applicable for Germany.

10.11.18 Greece

- Section 5.2, exclusion criterion #3 and Appendix 4 (Section 10.4.2): Contraceptive measures considered adequate include highly effective contraceptive methods in accordance with the CTFG (Clinical Trial Facilitation Group): Recommendations related to contraception and pregnancy testing in clinical studies.[68] This means use of double barrier methods is not applicable for Greece.

10.11.19 Hungary

- Sections 1.2, 5.1 and 8.9: Date of birth: participant's full date of birth is not allowed to be collected and must be shortened to year of birth.

10.11.20 India

No country-specific requirements apply.

10.11.21 Ireland

- Section 5.2, exclusion criterion #3 and Appendix 4 (Section 10.4.2): Contraceptive measures considered adequate include highly effective contraceptive methods in accordance with the CTFG (Clinical Trial Facilitation Group): Recommendations related to contraception and pregnancy testing in clinical studies.[68] This means use of double barrier methods is not applicable for Ireland.

10.11.22 Israel

- Section 6.6: At the end of the study, participants may continue to receive investigational product (IMP) free of charge for a period of 3 years subject to the conditions outlined in the Israeli Ministry of Health "Procedure for Clinical Trials in Human Subjects".
- Section 8.7 and 8.8, Appendix 5 (Section 10.5) and Appendix 7 (Section 10.7): No participants from Israel will participate in the optional biobank part of the study where collected samples will be used for future research, and no genetic testing will be performed.

10.11.23 Italy

- Section 5.2, exclusion criterion #3 and Appendix 4 (Section 10.4.2): Contraceptive measures considered adequate include highly effective contraceptive methods in accordance with the CTFG (Clinical Trial Facilitation Group): Recommendations related to contraception and pregnancy testing in clinical studies.[68] This means use of double barrier methods is not applicable for Italy.
- Section 1.2 and 8.2.9 Pregnancy testing: Monthly testing with highly sensitive urine pregnancy tests is required for WOCBP in Italy.

10.11.24 Japan

- Section 6.2: Preparation/Handling/Storage/Accountability: The head of the study site or storage manager assigned by the head of the study site (a pharmacist in principle) is responsible for control and accountability of the study intervention, in accordance with Japanese GCP.
- Appendix 1 (Section 10.1.1), Regulatory and ethical considerations: A name or a seal is accepted as a signature.

10.11.25 Latvia

- Section 5.2, exclusion criterion #3 and Appendix 4 (Section 10.4.2): Contraceptive measures considered adequate include highly effective contraceptive methods in accordance with the CTFG (Clinical Trial Facilitation Group): Recommendations related to contraception and pregnancy testing in clinical studies.[68] This means use of double barrier methods is not applicable for Latvia.
- Sections 5.2 (exclusion criterion #26) and 8.2.7 (tuberculosis screening): All participants must undergo testing for latent TB with a central lab QuantiFERON-TB test unless the participant has a QuantiFERON-TB or T-SPOT.TB test no more than 90 days old at screening (visit 1), documented in medical records.
- Sections 1.2 and 8.2.7, TB monitoring: Participants should undergo yearly TB testing during the entire study to take into account the epidemiological situation of tuberculosis in Latvia and the duration of the study. The TB test for monitoring should be performed locally and both the TB skin tests (not suitable for BCG vaccinated participants) and interferon-gamma release assays (e.g., QuantiFERON-TB) may be used depending on local availability.

10.11.26 Lithuania

- Sections 1.2, 5.1 and 8.9: Date of birth: participant's full date of birth is not allowed to be collected and must be shortened to year of birth.
- Sections 5.2 (exclusion criterion #26) and 8.2.7 (tuberculosis screening): All participants must undergo testing for latent TB with a central lab QuantiFERON-TB test unless the participant has a QuantiFERON-TB test no more than 90 days old at screening, documented in medical records (no more than 90 days old at screening). Participants who have previously been treated for active or latent tuberculosis should not be monitored using TB tests as the tests are likely to remain positive even after successful treatment. These subjects should instead be monitored based on signs or symptoms.
- Section 5.2, Exclusion criterion #25: All Lithuanian patients with a diagnosis of human immunodeficiency virus (HIV) should be excluded from the study, irrespectively of treatment.

10.11.27 Macedonia

No country-specific requirements apply.

10.11.28 Malaysia

No country-specific requirements apply.

10.11.29 Mexico

- Section 7.2: Should the participant, his/her family members, parents or legal representative decide to withdraw the consent for participation in the study, the participant will be entitled to receive appropriate, free of charge medical care and/or product during the follow up period of the protocol when it will be established with certainty that no untoward medical consequences of the participant´s participation in the research occurred.
- Appendix 1 (Section 10.1.1): In the case of Mexico, the following responsibilities will be included for the head of the Institution/Health Care Establishment, Ethics, Research and, when applicable, Biosafety Committees and Novo Nordisk within their scope of responsibility:

- Investigation follow-up.
- Damages to health arising from the investigation development; as well as those arising from interruption or advanced suspension of treatment due to non-attributable reasons to the participant.
- Timely compliance of the terms in which the authorisation of a research for health in human beings had been issued.
- To present in a timely manner the information required by the Health Authority.

- Appendix 1 (Section 10.1.13), Indemnity statement:
  - Novo Nordisk carries product liability for its products assumed under the special laws, acts/and/or guidelines for conducting studies in any country, including those applicable provisions on the Mexican United States. If the participant feels that something goes wrong during the course of this study, the participant should contact the study staff in the first instance.
  - If during their participation in the study the participant experiences a disease or injury that, according to the study doctor and Novo Nordisk, is directly caused by the study intervention and/or a study procedure that otherwise would not have been part of his/her regular care, the participant will receive from the Institution or Medical Care Establishment and free of charge, the appropriate medical treatment as required. In this case, the costs resulting from such treatment as well as the costs of any indemnification established by law will be covered by Novo Nordisk in accordance with the terms provided by all applicable regulations; even if the participant discontinues his/her participation in the study by his own will or by a decision from the investigator.
  - By signing the informed consent, the participant will not renounce to any compensation or indemnification he/she may be entitled to by law, nor will he/she will incur any additional expense as a result of his/her participation in the study; any additional expense resulting from the participant's participation in the study will be covered by Novo Nordisk.

10.11.30 Netherlands

- Sections 1.2, 5.1 and 8.9: Full day of birth can only be used if there is a strong need related to the hypothesis of the trial. Generally only year of birth (YoB) is to be used.

10.11.31 Norway

- Section 5.2, exclusion criterion #3 and Appendix 4 (Section 10.4.2): Contraceptive measures considered adequate include highly effective contraceptive methods in accordance with the CTFG (Clinical Trial Facilitation Group): Recommendations related to contraception and pregnancy testing in clinical studies.[68] This means use of double barrier methods is not applicable for Norway.
- Section 8.8: For Norway the analyses to be done must be specified and limited to related diagnoses or medical conditions, e.g., cardiovascular disease including heart failure, obesity, and diabetes.

10.11.32 Poland

- Sections 5.2 (exclusion criterion #3), 8.2.9 (Pregnancy testing) and Appendix 4 (Section 10.4.2): Contraception and pregnancy testing should be in accordance with the current EU

recommendations: Clinical Trials Facilitation and Coordination Group CTFG, Recommendations related to contraception and pregnancy testing in clinical trials Version 1.1.[68]

- Appendix 1 (Section 10.1.13), Indemnity statement: Novo Nordisk carries liability for the study exclusively in the scope defined by the applicable laws.

10.11.33 Portugal

- Sections 1.2, 5.1 and 8.9: Date of birth: participant's full date of birth is not allowed to be collected and must be shortened to year of birth.
- Sections 1.2 and 8.2.9: Monthly testing with highly sensitive urine pregnancy tests are required for WOCBP.
- Section 4.4.1: Section describes the option of using a search agency to facilitate identifying updated contact details for a missing participant or provide vital status (dead or last alive date). Providing patient's personal data to a third party for the purposes of a clinical study is not permitted in Portugal.
- Section 5.2, exclusion criterion #3 and Appendix 4 (Section 10.4.2): Contraceptive measures considered adequate include highly effective contraceptive methods in accordance with the CTFG (Clinical Trial Facilitation Group): Recommendations related to contraception and pregnancy testing in clinical studies.[68] This means use of double barrier methods is not applicable for Portugal.
- Sections 6.1.3 and 8: Download of study apps to the participants' smartphones is not allowed in Portugal. Hence, all participants from Portugal will be provided with a device on which the study app has been preloaded. No apps can be downloaded to the provided phone by the participant or the site. The provided phones come with no cost to the participant.
- Section 6.6: Participants from Portugal will have post-study access to the IMP until approval by the National Health Service if the investigator considers that the patient is benefiting from it.

10.11.34 Romania

- Sections 1.2 and 8.2.9: Monthly testing with highly sensitive urine pregnancy tests are required for WOCBP.
- Section 5.2, exclusion criterion #3 and Appendix 4 (Section 10.4.2): Contraceptive measures considered adequate include highly effective contraceptive methods in accordance with the CTFG (Clinical Trial Facilitation Group): Recommendations related to contraception and pregnancy testing in clinical studies.[68] This means use of double barrier methods is not applicable for Romania.

10.11.35 Serbia

No country-specific requirements apply.

10.11.36 Singapore

- Section 5.1, inclusion criterion #2: Legal age above or equal to 21 years at the time of signing informed consent.

10.11.37 Slovakia

- Appendix 1, Section 10.1.1: Regulatory and ethical considerations:
  The investigator will be responsible for:
  - notifying the IRB/IEC of SAEs – only death, as required by IRB/IEC procedures and local regulations
  - providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations
  - reporting any potential serious breaches to the sponsor immediately after discovery

  The sponsor will be responsible for:
  - providing written summaries of the status of the study annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC and/or regulatory authorities
  - notifying the IRB/IEC of SAEs or other significant safety findings according to local regulations and procedures established by the IRB/IEC and/or regulatory authorities ensuring submission of protocol, protocol amendments, ICF, investigator brochure, CSR synopsis and other relevant documents to the IRB/IEC and/or regulatory authorities.

10.11.38 Slovenia

No country-specific requirements apply.

10.11.39 South Africa

- Section 6.6: Participants shall have access to the investigational product for a minimum of 4 years after completion of the study in accordance with the SAHPRA guidelines ‘Post Clinical Trial Access, April-19_v2-1’.
- Sections 8.7 and 8.8, Appendix 5 (Section 10.5) and Appendix 7 (Section 10.7): No participants from South Africa will participate in the optional biobank part of the study where collected samples will be used for future research, and no genetic testing will be performed.

10.11.40 South Korea

- Sections 1.2, 5.2 (exclusion criterion #3), 8.2.9, 10.2: Pregnancy testing: Serum test must be performed at the local or central laboratory at visit 1 and 2 for WOCBP, at the discretion of the investigator.
- Section 5.1, inclusion criterion #2: Legal age above or equal to 19 years at the time of signing informed consent.
- Section 5.1 (inclusion criteria #3 and 4): Footnote a is not applicable for South Korea: Patients referred from the prevalence study (NN6018-7527) are not eligible to be enrolled based on their hs-CRP and/or NT-proBNP (requiring corresponding ECG from the same date) results obtained in the prevalence study.
- Sections 6.2.1 (Dispensing of study intervention administration) and 6.2.5 (Shipment of study intervention to participant’s home/residence/location) by courier service or collecting the allocated study intervention on behalf of the participant by non-participating person. According to HA regulation, this possibility is only allowed in South Korea if a participant is under self-quarantine due to COVID-19 infection.

- Section 8.7 and 8.8, Appendix 5 (Section 10.5) and Appendix 7 (Section 10.7): No participants from South Korea will participate in the optional biobank component of the study where collected samples will be used for future research, and no genetic testing will be performed.

10.11.41 Spain

- Sections 1.2, 5.1 and 8.9: Date of birth: participant's full date of birth is not allowed to be collected and must be shortened to year of birth.
- Section 5.2, exclusion criterion #3 and Appendix 4 (Section 10.4.2): Contraceptive measures considered adequate include highly effective contraceptive methods in accordance with the CTFG (Clinical Trial Facilitation Group): Recommendations related to contraception and pregnancy testing in clinical studies.[68] This means use of double barrier methods is not applicable for Spain.
- Section 8.9: Race and ethnicity are not allowed to be collected by local regulation.
- Appendix 1 (Section 10.1.10): Retention of clinical study documentation: 25 years according to the new Spanish Royal Decree 1090/2015.

10.11.42 Taiwan

- Sections 1.2, 5.1 and 8.9: Date of birth: participant's full date of birth is not allowed to be collected and must be shortened to month and year of birth.
- Section 10.1.3, Informed consent process: Study participants must be re-consented to the most current version of the informed consent forms during their participation in the study according to sponsors instructions. The IRB will review the informed consent form amendment and decide whether the re-consent can be waived. Participants may not need to be re-consented if the change of the informed consent form is administrative.

10.11.43 Thailand

- Section 5.2, exclusion criterion #3 and Appendix 4 (Section 10.4.2): Contraceptive measures considered adequate include highly effective contraceptive methods in accordance with the CTFG (Clinical Trial Facilitation Group): Recommendations related to contraception and pregnancy testing in clinical studies.[68] This means use of double barrier methods is not applicable for Thailand.

10.11.44 Turkey

- Section 6.4.3: In case a participant needs to initiate a new treatment or change their regular dose of a concomitant medication due to a protocol requirement, this medication will be reimbursed by Novo Nordisk.
- Section 6.6: Participants may receive post-study access to the investigational product if:
  - the benefit/risk ratio is favourable for the participants and no satisfactory treatment is available on the market in Turkey,
  - the competent Turkey health authorities approve this access, and
  - the development and manufacturing of the IMP is continued.

10.11.45 United Kingdom

- Sections 1.2 and 8.2.9 (Pregnancy testing): Monthly testing with highly sensitive urine pregnancy tests are required for WOCBP.
- Appendix 1 (Section 10.1.5): In the United Kingdom the IRB/IEC does not have access to the participants' medical records.
- Section 5.2, exclusion criterion #3 and Appendix 4 (Section 10.4.2): Contraceptive measures considered adequate include highly effective contraceptive methods in accordance with the CTFG (Clinical Trial Facilitation Group): Recommendations related to contraception and pregnancy testing in clinical studies.[68] The use of double barrier method is not acceptable for United Kingdom as the sole means of contraception but may be used as a form of additional contraception in addition to the highly effective methods listed in Table 10-3.
- Sections 5.6 (Assessment of eligibility) and 7.1.1 (Study intervention discontinuation criteria): Participants randomised in violation of inclusion and exclusion criteria are to be withdrawn from study intervention.
- Section 6.6: Participants may receive post-study access to the investigational product if:
  - the benefit/risk ratio is favourable for the participants and no satisfactory treatment is available on the market in the United Kingdom,
  - the competent United Kingdom health authorities approve this access, and
  - the development and manufacturing of the IMP is continued.

10.11.46 United States of America

- Appendix 1 (Section 10.1.1), Regulatory, ethical, and study oversight considerations. All US investigators, from US sites conducted under the IND, will sign FDA Form 1572. All investigators outside of the US, including participating sites outside the US not conducted under the IND, will not sign FDA form 1572. Novo Nordisk will analyse and report data from all sites together if more than one site is involved in the study.

10.12 Appendix 12: Abbreviations and terms

ACS	acute coronary syndrome	H_0	null hypothesis
ADA	anti-drug-antibodies	H_A	alternative hypothesis
AE	adverse event	HbA_{1c}	glycated haemoglobin
AF	atrial fibrillation	HDL	high-density lipoprotein (cholesterol)
ALT	alanine aminotransferase	HF	heart failure
ASCVD	atherosclerotic cardiovascular disease	HF event	heart failure event comprising heart failure hospitalisation and urgent heart failure visit
AST	aspartate aminotransferase	composite HF endpoint	endpoint comprising CV death and HF events
ARNi	Angiotensin Receptor-Neprilysin inhibitor	HFmrEF	heart failure with mildly reduced ejection fraction
BCG	bacille Calmette-Guerin (vaccine for TB)	HFpEF	heart failure with preserved ejection fraction
CI	confidence interval	HFrEF	heart failure with reduced ejection fraction
CKD	chronic kidney disease	HIV	human immunodeficiency virus
CKD-EPI	chronic kidney disease – epidemiology collaboration	HR	hazard ratio
COPD	chronic obstructive pulmonary disease	HRT	hormone replacement therapy
CV	cardiovascular	hs-CRP	high-sensitivity C-reactive protein
CVD	cardiovascular disease	IB	investigator's brochure
CRF	case report form	ICH	International Council for Harmonisation
CRP	C-reactive protein	IEC	independent ethics committee
CTFG	Clinical Trial Facilitation Group	IL-1β	interleukin-1 beta
CSR	clinical study report	IL-6	interleukin 6
CVOT	cardiovascular outcome trial	IMP	investigational medicinal product
CYP	cytochrome (P450 or 3A4)	INR	international normalised ratio
DBL	data base lock	IRB	institutional review board
DFU	directions for use	i.v.	intravenous(ly)
DILI	Drug-induced liver injury	KCCQ	Kansas City Cardiomyopathy Questionnaire
DMARD	disease modifying anti-rheumatic drugs	LA	Left atrial
DMC	data monitoring committee	LAIV	live attenuated influenza vaccine
DNA	deoxyribonucleic acid	LAR	legally acceptable representative
DUN	dispensing unit number	LDL	low-density lipoprotein (cholesterol)
EAC	event adjudication committee	LV	left ventricular
EAS	event adjudication system	LVAD	left ventricular assist device
ECG	electrocardiogram	LVEF	left ventricular ejection fraction
eCRF	electronic case report form	LVEDD	left ventricular end diastolic dimension
eGFR	estimated glomerular filtration rate	LVEDP	left ventricular end diastolic pressure
EoT	end of treatment visit	LVM	left ventricular mass
ePRO	electronic patient reported outcome	LPLV	last participant last visit
EQ-5D-5L	European Quality of Life five Dimensions five Level	LTFU	lost to follow-up
FAS	full analysis set	MACE	Major adverse cardiovascular event
FDA	U.S. Food and Drug Administration	MAP	modelling analysis plan
FDAAA	FDA Amendments Act	MCH	mean corpuscular haemoglobin
FU	follow-up	MCHC	mean corpuscular haemoglobin concentration
GCP	Good Clinical Practice	MCV	mean corpuscular volume
GEP	global expert panel	MI	myocardial infarction
GLP-1 RA	glucagon-like peptide-1 receptor agonist	MMRV	measles, mumps, rubella, and varicella

List is continued on the next page

mos	months	SAE	serious adverse event
MR	ratio of the mean number of events between ziltivekimab and placebo	SAP	statistical analysis plan
NOAEL	no-observed-adverse-effect level	s.c.	subcutaneously
NT-proBNP	N-terminal-pro-brain natriuretic peptide	SF-36	short form 36 health survey
NYHA	New York Heart Association	SGLT-2i	sodium glucose cotransporter-2 inhibitor
p	probability	SIF	safety information form
PCD	primary completion date	SPFQ	(TransCelerate) subject participation feedback questionnaire
PCI	percutaneous coronary intervention	StC	steering committee
PCS	physical component score in SF-36	SUSAR	suspected unexpected serious adverse reaction
PD	pharmacodynamics	TB	tuberculosis
PGI-C	Patient Global Impression of Change	TMM	trial materials manual
PGI-S	Patient Global Impression of Severity	ULN	upper limit of normal (reference range)
PK	pharmacokinetics	V	visit
Q4W	every four weeks	VAS	visual analogue scale
RNA	ribonucleic acid	WOCBP	woman of childbearing potential
RTSM/IWRS	Randomisation and Trial Supply Management/Interactive Web Response System		

10.13 Appendix 13: Protocol amendment history

The protocol amendment summary of changes table for the current protocol version is located directly before the table of contents.

10.13.1 Protocol version 3.0: 03 April 2023

This amendment is considered to be non-substantial for all countries based on the criteria set forth in Article 2(13) of Regulation (EU) No 536/2014 of the European Parliament and the Council of 16 April 2014;[1] because it neither substantially impacts the safety or rights of the participants nor the reliability or robustness of the data generated in the study.

Overall rationale for preparing protocol, version 3.0:

Document has been revised to implement global changes requested during request for information by EU health authorities and independent ethics committees. In addition, country/region-specific requirements for Bulgaria, France, Italy, Lithuania, Norway, and Portugal have been updated.

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Section # and name	Description of change	Rationale
Section 1.2 Flowchart	Footnote e updated to include a reference to country-specific requirements for Lithuania.	To accommodate local requirements for only collecting year-of-birth in Lithuania.
Section 1.2 Flowchart	Footnote h updated to include a reference to country-specific requirements for Italy.	To accommodate health authority request for monthly highly sensitive pregnancy testing of WOCBP in Italy.
Section 1.2 Flowchart	Footnote m updated: Note, this option is only available for selected countries based on CardioSignal app registration status *(Section 8.12.3)*. Participants should download the CardioSignal app at V2 and receive training in its use before collecting any data. The app should be used by the participants between visits, in accordance with agreements between the participant and investigator. Relevant findings from the app should be discussed with the participant at a visit, and appropriate actions should be taken at the discretion of the investigator. *Local requirements may apply. Portugal: see country/region-specific requirements (Appendix 11, Section 10.11).*	To specify further and comply with local requirements in Portugal.
Section 1.2 Flowchart	Hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), hepatitis B virus (HBV), pharmacodynamic (PD), and tuberculosis (TB) added to abbreviations list.	For correctness.
Section 4.4.1 End of study assessments	Updated to include references to country-specific requirements for France and Portugal.	Providing patient's personal data to a third party for the purposes of a clinical study is not permitted in Portugal.

Section # and name	Description of change	Rationale
		Obtaining health information from publicly available source is not permitted in France.
Section 5.1 Inclusion criteria	Updated to include a reference to country-specific requirements for Lithuania.	To accommodate local requirements for only collecting year-of-birth in Lithuania.
Section 5.2 Exclusion criteria	Updated to include a reference to country-specific requirements for France.	To accommodate local requirements for exclusion of incapacitated patients, protected minors and patients in emergency situation in France.
Section 6.1.3 Other study supplies including non-investigational medical device	Updated to include a reference to country-specific requirements for Portugal.	All participants from Portugal will be provided with a device on which the study app has been preloaded.
Section 6.6 Continued access to study intervention after end of study	Updated to include references to country-specific requirements for France and Portugal.	To accommodate local requirements for post-study access to the IMP.
Section 7.3 Lost to follow-up	Text modified: • Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, at least three telephone calls and, if necessary, a certified letter to the participants' last known mailing address or local equivalent methods, as described in Section 4.4.1). These contact attempts should be documented in the participant's source document. *Contact attempts will be made in accordance with local legislation.*	To further clarify that contact attempts will be made in accordance with local legislation.
Section 7.3 Lost to follow-up	Updated to include a reference to country-specific requirements for France.	Obtaining health information from publicly available source is not permitted in France.

Section # and name	Description of change	Rationale
Section 8 Study assessments and procedures	Updated to include a reference to country-specific requirements for Portugal.	All participants from Portugal will be provided with a device on which the study app has been preloaded.
Section 8.2.9 Pregnancy testing	Updated to include a reference to country-specific requirements for Italy.	To accommodate health authority request for monthly highly sensitive pregnancy testing of WOCBP in Italy.
Section 8.8 Biomarkers	Updated to include a reference to country-specific requirements for Norway.	To accommodate local requirements for collection of biosamples in Norway.
Section 8.9 Demography and other baseline assessments	Updated to include a reference to country-specific requirements for Lithuania.	To accommodate local requirements for only collecting year-of-birth in Lithuania.
Section 8.12.3 Cardio Signal app	Text modified: Study participants, with no history of permanent atrial fibrillation, will be invited to use a digital biomarker and monitoring solution, the CardioSignal app *('MyCardioSignal' in the United States)*. Note, this option is only available for selected countries *(i.e., Austria, Belgium, Denmark, Finland, France, Germany, India, Italy, Ireland, Spain, the United Kingdom, and the United States)* based on registration status.	For clarification
Section 10.7.3 Hypersensitivity reaction samples	Text modified: The samples will be ~~anonymised~~ *pseudonymised* (identified only by subject ID, visit number, study identification number and sampling date). Confidentiality and personal data protection will be ensured during storage after the end of study and no direct identification of the participant will be stored together with the samples.	For correctness
Section 10.10.1 Visits	Updated to include a reference to country-specific requirements for Bulgaria.	To accommodate local requirements for home visits in Bulgaria.
Section 10.11.7 Bulgaria	Requirements for Bulgaria added: • *Section 10.10.1: Home visits are not applicable to Bulgaria.*	To comply with local requirements in Bulgaria.
Section 10.11.16 France	Requirements for France added: • *Section 4.4.1 and 7.3: It is not permitted to obtain health information from publicly available sources in France.* • *Section 5.2 (exclusion criterion #6): According to French regulation (CSP art 1121 5, 7 and 12), incapacitated patients, protected minors and patients in emergency situation are not*	To comply with local requirements in France.

Section # and name	Description of change	Rationale
	eligible for participation in clinical studies in France. • *Section 6.6: If at the end of the study the participant has a beneficial effect from the study medicine, the investigator may, in agreement with the sponsor, decide to continue the treatment through an ATU request (temporary authorisation for use) before the study medication is potentially marketed.*	
Section 10.11.23 Italy	Requirements for Italy added: • *Section 1.2 and 8.2.9 Pregnancy testing: Monthly testing with highly sensitive urine pregnancy tests is required for WOCBP in Italy.*	To comply with local requirements in Italy.
Section 10.11.26 Lithuania	Requirements for Lithuania added: • *Sections 1.2, 5.1 and 8.9: Date of birth: participant's full date of birth is not allowed to be collected and must be shortened to year of birth.*	To comply with local requirements in Lithuania.
Section 10.11.31 Norway	Requirements for Norway added: • *Section 8.8: For Norway the analyses to be done must be specified and limited to related diagnoses or medical conditions, e.g., cardiovascular disease including heart failure, obesity, and diabetes.*	To comply with local requirements in Norway.
Section 10.11.33 Portugal	Requirements for Portugal added: • *Section 4.4.1: Section describes the option of using a search agency to facilitate identifying updated contact details for a missing participant or provide vital status (dead or last alive date). Providing patient's personal data to a third party for the purposes of a clinical study is not permitted in Portugal.* • *Sections 6.1.3 and 8: Download of study apps to the participants' smartphones is not allowed in Portugal. Hence, all participants from Portugal will be provided with a device on which the study app has been preloaded. No apps can be downloaded to the provided phone by the participant or the site. The provided phones come with no cost to the participant.* • *Section 6.6: Participants from Portugal will have post-study access to the IMP until approval by the National Health Service if the investigator considers that the patient is benefiting from it.*	To comply with local requirements in Portugal.

10.13.2 Protocol version 2.0: 07 February 2023

This amendment is considered to be non-substantial for all countries based on the criteria set forth in Article 2(13) of Regulation (EU) No 536/2014 of the European Parliament and the Council of 16

April 2014;[1] because it neither substantially impacts the safety or rights of the participants nor the reliability or robustness of the data generated in the study.

Overall rationale for preparing protocol, version 2.0:

Document has been revised to update country-specific requirements for Argentina, Japan, and South Korea.

Deleted text is written as ~~strikethrough~~ and new text *italic*.

Section # and name	Description of change	Rationale
Section 1.2 Flowchart (footnote h)	Updated to include a reference to country-specific requirements for South Korea	To accommodate local requirements for pregnancy testing in South Korea
Section 5.1 Inclusion criteria	Updated to include a reference to country-specific requirements for South Korea.	To accommodate local requirements in South Korea.
Section 5.2 Exclusion criteria	Reference to country-specific requirements for Japan removed	To comply with local requirements in Japan
	Updated to include a reference to country-specific requirements for South Korea	To accommodate local requirements for pregnancy testing in South Korea.
Section 6.2.1 Dispensing of study intervention administration	Updated to include references to country-specific requirements for South Korea	To accommodate local requirements in South Korea
Section 6.2.4 Accountability of study intervention	Reference to country-specific requirements for South Korea removed	For correctness
Section 6.2.5 Shipment of study intervention to participant's home/residence/location	Updated to include a reference to country-specific requirements for South Korea	To accommodate local requirements in South Korea
Section 8.2.7 Tuberculosis screening	Updated to include a reference to country-specific requirements for Argentina	To accommodate local requirements in Argentina
Section 8.2.9 Pregnancy testing	Updated to include a reference to country-specific requirements for South Korea	To accommodate local requirements for pregnancy testing in South Korea
Section 10.2 Appendix 2: Clinical laboratory tests, Table 10-2 (footnote d)	Updated to include a reference to country-specific requirements for South Korea	To accommodate local requirements for pregnancy testing in South Korea
Section 10.11.1 Appendix 11: Country-specific requirements for Argentina	Criterion for Argentina added:	To accommodate local requirements in Argentina

Section # and name	Description of change	Rationale
	• *Sections 5.2 (exclusion criterion #26) and 8.2.7 (tuberculosis screening): All participants in Argentina must undergo testing for latent TB with a central lab QuantiFERON-TB test unless the participant has a QuantiFERON-TB test or T-SPOT.TB test no more than 90 days old at screening (visit 1), documented in medical records.*	
Section 10.11.24 Appendix 11: Country-specific requirements for Japan.	Criterion for Japan omitted: ~~Section 5.2, exclusion criterion #14: Uncontrolled hypertension (defined as an average systolic blood pressure ≥160 mm Hg or an average diastolic blood pressure ≥100 mm Hg) at screening (visit 1).~~	For correctness
Section 10.11.40 Appendix 11: Country-specific requirements for South Korea	Requirements for South Korea added: • *Sections 1.2, 5.2 (exclusion criterion #3), 8.2.9, 10.2: Pregnancy testing. Serum test must be performed at the local or central laboratory at visit 1 and 2 for WOCBP, at the discretion of the investigator.* • *Section 5.1 (inclusion criteria #3 and 4): Footnote a is not applicable for South Korea: Patients referred from the prevalence study (NN6018-7527) are not eligible to be enrolled based on their hs-CRP and/or NT-proBNP (requiring corresponding ECG from the same date) results obtained in the prevalence study.* • *Sections 6.2.1 (Dispensing of study intervention administration) and 6.2.5 (Shipment of study intervention to participant's home/residence/location) by courier service or collecting the allocated study intervention on behalf of the participant by non-participating person. According to HA regulation, this possibility is only allowed in South Korea if a participant is under self-quarantine due to COVID-19 infection.*	To comply with local requirements in South Korea
	Requirement for South Korea removed: • ~~Section 6.2.4: If required by site policy, used and partially used study intervention can be discarded immediately after drug accountability and only unused study intervention and empty packaging will be stored until reconciliation by monitor. Empty packaging will be used for the monitor to perform reconciliation of used study intervention.~~	For correctness
Section 10.13 References	References renumbered: Previous reference #1 is now #2, and one new reference is added: *1. The European Parliament and the Council of the European Council of the European Union. Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. 27 May 2014.*	For alignment

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