STUDY PROTOCOL

Long-term treatment outcome of Pompe patients switched to Avalglucosidase alfa

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List of abbreviations

PD	Pompe disease
GAA	acid α-glucosidase
IOPD	infantile onset Pompe disease
LOPD	late onset Pompe disease
ERT	enzyme replacement therapy
ECHO-LVM Z-score	echocardiogram-left ventricular mass Z-score
CK	creatine kinase
Glc4/Hex4	oligosaccharides
AE	adverse event
RWE	Real-World Evidence
ODD	Orphan Drug Designation
FDC	focused data collection
MAP	Managed Access Program
QMFT	Quick Motor Function Test
SD	standard deviation
ALT	alanine aminotransferase
AST	aspartate aminotransferase
Ig	immunoglobulin
TEAE	treatment-emergent adverse event
IAR	infusion-associated reaction
CI	confidence interval
SE	standard error

1. Synopsis

Title of study	Long-term treatment outcome of Pompe patients switched to Avalglucosidase alfa
Location	Taiwan
Study centers	National Taiwan University Hospital
Expected study period	Three years, from Oct 2023 to Q3 2026
Objectives	Evaluate short- and long-term biomarker, motor function, respiratory function and safety with avalglucosidase alfa in IOPD and LOPD patients who switched from other ERT.
Methodology	Clinical characteristics of Pompe patients receiving avalglucosidase alfa will be collected and analyzed. Adverse events occurring during avalglucosidase alfa treatment will be collected and described. Urinary Glc4/Hex4 is the primary endpoints for effectiveness analysis of avalglucosidase alfa. Other assessment items include creatine kinase, motor function (Quick Motor Function Test) and respiratory function (forced vital capacity). The evolution of those assessment items after avalglucosidase alfa treatment will be descriptively analyzed and compared to baseline assessments (i.e., the time before initiating avalglucosidase alfa and/or one-year preceding avalglucosidase alfa initiation) at the individual patient level depending on prior duration of ERT at time of avalglucosidase alfa switch.
Number of patients	26
Population	Pompe Patients receiving Avalglucosidase alfa
Criteria for eligibility	Inclusion criteria: - IOPD patients >6 months who treated with alglucosidase alfa - LOPD patients who previously treated with ERT - Pompe patients for whom the physician has independently decided to prescribe avalglucosidase alfa - Patients or their legal representatives unable to or refusing

	to receive the recommended testing (Table 1) are used to identify as a potential subgroup of interest in exploratory analyses Exclusion criteria: - Patients or their legal representatives refusing to sign the inform consent form
Criteria for analysis	<u>Effectiveness assessment</u> • Data will be collected following the recommended schedule of assessments in Table 1. <u>Safety assessment</u> • Adverse events occurring during avalglucosidase alfa treatment will be collected and described.

Statistical methods	The main approach is a descriptive analysis, including spaghetti plots of the within-patient data over time. Depending on the number of patients enrolled and amount of available data at the time of each report, exploratory statistical analyses may be performed. The exploratory statistical analyses will be conducted with 2 parts: **<u>Part I</u>: Change from baseline (the time before initiating avalglucosidase alfa)** Analysis of Primary and secondary assessment items include urinary oligosaccharides, creatine kinase, motor function (Quick Motor Function Test) and respiratory function (forced vital capacity) for avalglucosidase alfa treatment at individual patient level: - Treatment outcomes will be evaluated based on the difference in endpoints between baseline and avalglucosidase alfa treatment for each patient. **<u>Part II</u>: Change from previous enzyme replacement treatment** Primary and secondary assessment items include creatine kinase, urinary oligosaccharides, motor function (Quick Motor Function Test) and respiratory function (forced vital capacity) for comparisons of avalglucosidase alfa to other ERT at individual patient level: - Differences between previous ERT and avalglucosidase alfa treatment will be calculated for each patient. - Treatment outcomes will be evaluated based on difference in slopes between two or more values of endpoints over time between the two treatments.

2. Abstract

Introduction: Pompe disease is a rare autosomal recessive disorder of glycogen metabolism due to a deficiency of acid α-glucosidase (GAA), characterized by intralysosmal storage of glycogen. While late onset Pompe disease (LOPD) can be identify through dry blood test. Patients with the classic infantile onset form of the disease (IOPD) can be recognized as early as the neonatal period with evidence of cardiac dysfunction, although typically there is evidence of rapidly progressive hypotonia, weakness, cardiomyopathy, and respiratory insufficiency. Enzyme replacement therapy using recombinant human GAA, alglucosidase alfa, is the only approved treatment for clinical use in patients with Pompe disease in Taiwan. The COMET phase 3 study and Mini-COMET phase 2 study demonstrates that treatment with avalglucosidase alfa is effective to stabilize or improve the clinical outcomes motor function, disease progress-related biomarkers including serum creatine kinase (CK) and urinary oligosaccharides (urinary Glc4/Hex4), and quality of life in Pompe patients.

Methods: Patients with a diagnosis of Pompe disease receiving avalglucosidase alfa will be included. Primary assessment item is urinary oligosaccharides. Secondary assessment items include creatine kinase, motor function (Quick Motor Function Test) and respiratory function (forced vital capacity). Changes of primary and secondary assessment items will be compared between baseline and after avalglucosidase alfa treatment at the individual patient level. For patients previously receiving ERT, slopes of changes between two or more values of each assessment items following treatment with other ERT and avalglucosidase alfa, respectively, will be compared intra-patiently. Adverse events (AE) will be collected and described by the event rate (as number of events divided by total of on-treatment patient-years of follow-up) and incidence rate (as number of patients with at least 1 AE). AEs will also be graded by severity (Grade 1-4) and ranked according to their frequency of occurrence.

3. Introduction

Pompe disease, also known as Type II glycogen storage disease, is a rare autosomal recessive neuromuscular disorder caused by mutations in the gene that encodes acid α-glucosidase (GAA). The lack or deficiency of lysosomal GAA, an enzyme required for lysosomal glycogen degradation leads to severe cardiac and skeletal muscle

myopathy due to progressive accumulation of glycogen (Meena & Raben, 2020). The broad clinical spectrum of Pompe disease depends on the age of onset. The severity of clinical manifestations, tissue impairment and age of onset correlate with the nature of mutations and the residual enzymatic activity levels. Pompe disease is classified into two forms: infantile onset (IOPD), considered as the classic form, and a late onset or non-classic form (LOPD), which can occur at young or adult age (Taverna et al., 2020). IOPD is more severe than LOPD and begins at birth or within the first few months of life. It is characterized by cardiomyopathy and muscle weakness, and it can cause death in the first year of life (van Capelle et al., 2016). A small percentage of patients show clinical signs with non-severe cardiomyopathy during the first year of life; this form of Pompe disease is referred to as non-classic IOPD (Gupta et al., 2020; van den Hout et al., 2003).

Alglucosidase alfa enzyme replacement therapy (ERT) using recombinant human GAA is approved worldwide for clinical use in patients with Pompe disease. Alglucosidase alfa has provided irrefutable clinical benefits, but has not been an optimal treatment primarily due to poor drug targeting of ERT to skeletal muscles (Do, Khanna, & Gotschall, 2019). Avalglucosidase alfa (neoGAA) is a next-generation, glycoengineered recombinant GAA replacement therapy with increased bis-mannose-6-phosphate (M6P) levels on the molecule in order to increase receptor-mediated uptake (Zhu et al., 2009; Zhu et al., 2005). The resultant neoGAA glyco-conjugate was shown to have significantly higher binding affinity for cation-independent M6P receptors and better muscle targeting, resulting in greater glycogen reduction in Gaa-KO mice as compared to alglucosidase alfa at equivalent dose (Zhu et al., 2009).

In human clinical trials, the primary support for the efficacy of avalglucosidase alfa in the treatment of Pompe disease comes from the pivotal randomized phase 3 study EFC14028 (COMET) comparing avalglucosidase alfa to alglucosidase alfa in the treatment of naïve LOPD patients. Additional evidence of efficacy comes from the phase 2 study ACT14132 (Mini-COMET) in previously treated IOPD patients > 6 months. The results of Mini-COMET study suggest that treatment with avalglucosidase alfa at 20 and 40 mg/kg qow is effective to stabilize or improve the

clinical outcomes of cardiac function assessed by echocardiogram-left ventricular mass Z-score (ECHO-LVM Z-score), motor function assessed by Gross Motor Function Measure-88 and Quick Motor Function Test, biomarkers indicative of disease progression including serum creatine kinase (CK) and urinary oligosaccharides (Glc4/Hex4), as well as quality of life in patients with IOPD previously treated with alglucosidase alfa within a range of different doses between 20 mg/kg qow and 42.6 mg/kg qw and who presented with clinical decline or suboptimal clinical response while receiving that dose regimen.

To substantiate the clinical evidence of avalglucosidase alfa in Pompe patients in a real-world clinical setting, we aim at collecting the real-world data to demonstrate the effectiveness and safety of avalglucosidase alfa in treatment naïve and ERT experienced Pompe patients in Taiwan.

4. Methods

4.1 Selection of population

4.1.1 Inclusion criteria:

- Confirmed GAA enzyme deficiency (any tissue source) and/or confirmed 2 pathogenic GAA gene variants Pompe patient
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4.1.2 Exclusion criteria:

- Having severe allergic reaction to avalglucosidase alfa.
- Patient/parent/legal guardian is not agreeing to provide signed informed consent, and the patient, if <18 years of age

4.2 Data collection

Data will be collected from patients receiving avalglucosidase alfa. Effectiveness assessment will be performed from patients who have received avalglucosidase alfa for at least 6 months. The flow chart of patient enrollment is shown in Figure 1. The duration of data collection and analysis to generate local RWE in patients with Pompe patients receiving avalglucosidase alfa is three years in total. The timeline of data collection has been started from 2023 Q3 until 2024 Q4. Baseline for avalglucosidase alfa-treated patients will be defined as the closest assessment/data prior to or after the

date of first treatment with avalglucosidase alfa. For patients previously treated with other ERT, data from a 1-year treatment period before switching to avalglucosidase alfa will be retrospectively collected, and a 2-month open window for data collection (i.e., 14 months) will be allowed. Before starting treatment of avalglucosidase alfa, there will be an open window of 3-4 months during which data collected will be used as baseline. Avalglucosidase alfa is expected to be reimbursed in 2023. Seven patients under Managed Access Program (MAP), which is a Sanofi program providing compassionate use avalglucosidase alfa to patients with life threatening disease, data collection has been started from May 2021.

Table 1 shows the schedule of assessments, based on input from physicians in Taiwan experienced in treating patients with Pompe disease.

Table 1 Data Collection for Patients Receiving Avalglucosidase Alfa: Schedule of Assessments

Assessments categories (unless otherwise noted)[a*]	Test/Assessment	Baseline (tests/assessments closest to the time of switching to avalglucosidase alfa)[b]	Frequency of follow-up tests/assessments
Primary Pompe disease therapy	Primary Pompe disease therapy status, first treatment, ongoing treatment, and changes in treatment	V	Record any changes
Antidrug antibody tests	Alglucosidase alfa IgG titer	V	Annually
	Alglucosidase alfa neutralizing antibodies	If needed[c]	If needed[c]
	Alglucosidase alfa IgE	If needed[d]	If needed[d]
	Avalglucosidase alfa IgG titer	V	Biannually
	Avalglucosidase alfa neutralizing antibodies	If needed[c]	If needed[c]
	Avalglucosidase alfa IgE	If needed[d]	If needed[d]
Laboratory tests	CK	V	Quarterly
	Urinary oligosaccharides (urinary Glc4/Hex4)	V	Quarterly
Cardiac function	Chest x-ray	V	Annually
	Electrocardiogram	V	Biannually
	Echocardiogram	V	Biannually
Pulmonary function[#]	Respiratory support (status, first use, and ongoing use)	V	Record any changes
	Forced vital capacity (FVC)	V	Biannually
	Maximal Inspiratory Pressure (MIP)	V	Biannually
	Maximal Expiratory Pressure (MEP)	V	Biannually
	Polysomnography (sleep study)	V	Annually
Motor and mental	Peabody Developmental Motor Scale,	V	Biannually

development tests (base on patients' age) [#]	Second Edition (PDMS-II)		
	Pediatric Evaluation of Disability Inventory specific for Pompe disease (Pompe-PEDI)	V	Biannually
	Quick Motor Function Test[e]	V	Biannually
	Lower Extremity Muscle Strength at Week 49 as Assessed by Hand-held Dynamometry (HHD)	V	Annually
	6-minute walk test[#]	V	Annually
Cognitive function (base on patients' age)[#]	Mental development index (MDI) of the Bayley Scales of Infant Development-II (BSID-II)	V	Annually
	Comprehensive Developmental Inventory for Infants and Toddlers (CDIIT)	V	Biannually
Growth	Weight and height	V	Quarterly
	Head circumference (patients aged <6 years)	V	Quarterly
Speech disorders	Speech evaluation	V	
	Swallowing study	V	
Death or discontinuation		Record any changes	
Safety	ADRs will be reported to Sanofi local pharmacovigilance (PV). Assessment of AEs/TEAEs, including IARs		

ADR=adverse drug reaction; CK=creatine kinase; FVC=forced vital capacity; IgE=immunoglobulin E; IgG=immunoglobulin G; NPP=named patient program; SGOT=serum glutamate oxaloacetate transaminase; SGPT=serum glutamate pyruvate transaminase.

[*]For data collected retrospectively for 1 year, a 2-month open window for data collection (i.e., 14 months) is allowed.

[#]Not all of these data will be available for IOPD patients at baseline and follow-up because of their young age.

[a]The following case report forms will be added to the Pompe Registry by May 2021:

- Avalglucosidase alfa as an Option for Primary Pompe Therapy
- Avalglucosidase alfa Antidrug Antibody testing, Including IgG, Neutralizing Antibodies, and IgE
- Quick Motor Function Test
- Bayley Scales of Infant and Toddler Development-4th edition (Bayley IV)

[b]Baseline for avalglucosidase alfa-treated patients is defined as the closest assessment/data prior to or after the date of first treatment with avalglucosidase alfa. The allowable window period is 3-4months.

[c]Neutralizing antibody tests are not recommended unless a medical suspicion develops on a case-by-case basis (eg, given clinical decline and/or very high antidrug IgG titers) that neutralizing antibodies may be present.

[d]Antidrug IgE antibody testing is not recommended unless there is a medical suspicion of acute hypersensitivity.

[e] The Quick Motor Function Test will be added to the Pompe Registry CRF by May 2021

[f] The 4th edition of the Bayley Scales of Infant and Toddler Development (Bayley IV) has recently been released. Currently the Pompe Registry CRF only contains only a page for recording Bayley results. Because it is anticipated that Registry sites around the world may gradually switch to the Bayley IV, the CRF will be revised to allow recording of either Bayley III or Bayley IV results (the test used should be noted).

[g] Patient ID numbers for both the Pompe registry and the avalglucosidase alfa NPP should be recorded.

4.2.1 Primary Assessment Items (Table 1)

Urinary Glc4/Hex4 is the primary endpoints for effectiveness analysis of avalglucosidase alfa. Urinary Glc4/Hex4 is usually elevated in Pompe patients and are sensitive though nonspecific biomarkers for diagnosis and monitoring of IOPD or LOPD (Kishnani et al., 2006; Li et al., 2021; Young et al., 2009).

4.2.2 Secondary Assessment Items (Table 1)

- Secondary assessment items include creatine kinase, motor function (Quick Motor Function Test) and respiratory function (forced vital capacity). Serum CK is usually elevated in Pompe patients and are sensitive though nonspecific biomarkers for diagnosis and monitoring of IOPD or LOPD (Kishnani et al., 2006; Li et al., 2021; Young et al., 2009). QMFT score is strongly correlated with proximal muscle strength, and significantly differentiated between patients with different levels of mobility (van Capelle et al., 2012), muscle function will be assessed by QMFT annually. Pulmonary function will be assessed by forced vital capacity. For infants, pulmonary function tests are difficult to administer and therefore data might be limited.
- Cardiac function: assessed by chest x-ray and electrocardiogram recommended to be assessed biannually. Chest X-ray in IOPD shows cardiomegaly, lung volume reduction and/or areas of atelectasis. Electrocardiogram shows cardiomyopathy with ventricular hypertrophy and heart rhythm disorders; short P-R interval, and very wide QRS complex (Bay et al., 2019);
- Pulmonary function: polysomnography is recommended to be assessed annually, and respiratory support (status, first use, and ongoing use; record any changes). For infants, pulmonary function tests are difficult to administer and therefore

data may be limited.

- Motor function: assessed by 6-minute walk test, and ambulatory status (record any changes). Many of these motor function assessments will have limited, if any, data in infancy/early childhood.
- Development: assessed by Bayley Scales of Infant and Toddler Development III (or IV) annually; growth including weight and height, and head circumference for patients aged < 6 years (recommended to be measured quarterly); death or discontinuation (record any changes).
- Primary PD therapy: including primary PD therapy status, first treatment, ongoing treatment, and changes in treatment (record any changes).
- ECHO-LVM Z-score will be measured biannually to assess left ventricular hypertrophy. Z-score is an indicator of how far a patient exceeds the mean LVM in normal subjects. Patients with LVM Z-score > 2 standard deviation (SD) are considered to have left ventricular hypertrophy (Colan, 2009; Kishnani et al., 2006).
- Immunogenicity: antidrug antibody tests.
- Safety: Adverse events occurring during avalglucosidase treatment will be collected and described by the event rate (as number of events divided by total of on-treatment patient-years of follow-up) and incidence rate (as number of patients with at least 1 AE). AEs will also be graded by severity (Grade 1-4) and ranked according to their frequency of occurrence.

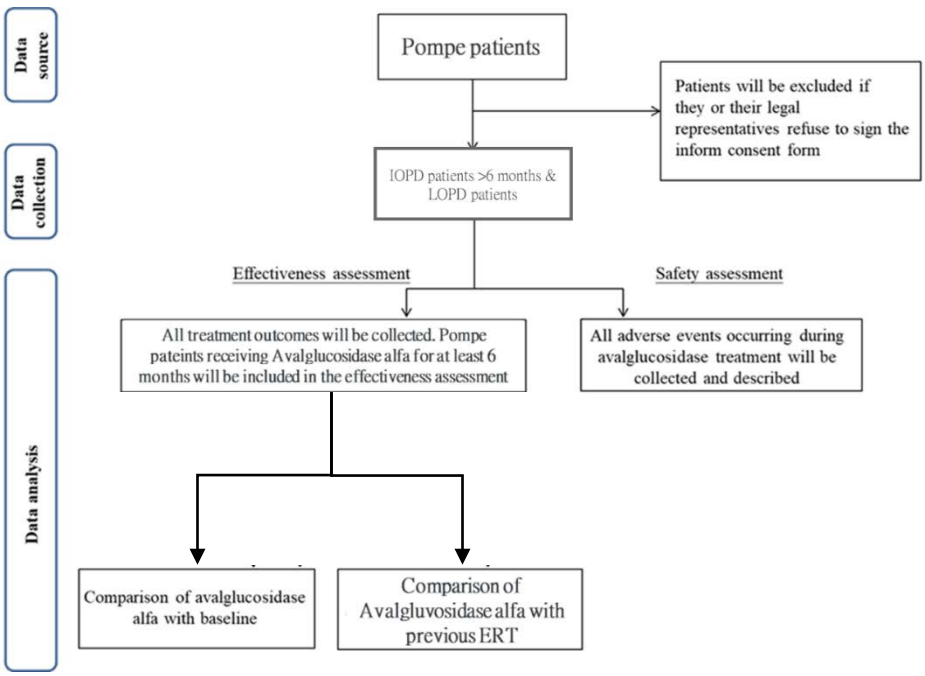


Figure 1. Data source for the analysis plan. Pompe patients receiving avalglucosidase alfa will be included for data collection regardless of whether they have previously received ERT. Pompe patients or their legal representatives who refuse to sign the inform consent forms will be excluded. Only data collected from patients who have received avalglucosidase alfa for at least 6 months will be included in the effectiveness assessment. All adverse events occurring during avalglucosidase treatment will be collected and described. Comparison of avalglucosidase alfa with baseline will be performed to evaluate treatment outcome. For patients previously receiving other ERT, intra-patient comparison of avalglucosidase alfa with other ERT will also be performed to evaluate treatment outcome.

4.3 Statistical analysis

The number of patients expected to be enrolled and analysed is 26 patients who treated with ERT or enrolled in managed access program. Patients' baseline clinical characteristics, primary and secondary assessment items at each time point will be described by mean, SD, confidence intervals (CIs), quartiles (i.e., 25^{th} and 75^{th} percentiles, median, inter-quartile range) for continuous variables or by frequencies and percentage for categorical variables. Several figures will be used to present continuous variables. Box plots will be used for presenting quartile information, maximum and minimum values. Bar charts will be used to present mean values with CI, SD, or SEs (standard errors). If data are collected at multiple time points, line chart with CI, SD, or SEs will be used to present mean values and their interval estimators. Grouped bar charts are also suitable to describe data with multiple time points or are used to present mean values grouped by other covariates. For categorical variables, bar charts or grouped bar charts will be used to describe numbers/frequencies or percentages.

4.3.1 Primary assessment items analysis for avalglucosidase alfa treatment at individual patient level:

The main approach is a descriptive analysis, including spaghetti plots of the within-patient data over time during avalglucosidase treatment in treatment naïve patients and during other ERT and avalglucosidase alfa treatment in switch patients. Depending on the number of patients enrolled and amount of available data at the time of each report, exploratory statistical analyses may be performed. For all statistical testing in exploratory analyses, p-values < 0.05 will be considered as

statistically significant.

CK, urinary Glc4/Hex4, and QMFT score will be treated as continuous variables. Mean values and SDs of CK and urinary Glc4/Hex4, routinely assessed, will be presented by spaghetti plots, and line graphs with interval estimators (e.g., CI, SD, or SE) may be considered if available data is allowed. For CK and urinary Glc4/Hex4 after 1 year of treatment, LVM Z-score and QMFT score, measured biannually or annually, bar charts or grouped bar charts will be used to illustrate the means values and their corresponding interval estimators. Change between baseline and avalglucosidase alfa treatment will be calculated for each patient and presented by a waterfall plot. Data of multiple time points will be analyzed separately. Wilcoxon signed rank test will be performed to examine whether there is statistical difference in primary endpoints between baseline and each time point during treatment with avalglucosidase alfa. Comparisons of parameters of interest at baseline and at time points during avalglucosidase alfa treatment will be performed to evaluate whether the disease is improved, stabilized or has declined. Improvement, stabilization, and decline will be categorized based on the difference in outcomes. Cut-off points will be defined according to the distribution of data collected. Improvement, stabilization, or decline of CK, urinary Glc4/Hex4, QMFT and LVM Z-score is dependent on both the actual magnitude of the change from baseline and the sample size. Results of status of change in outcomes will be summarized as n (%) and presented in bar charts.

4.3.2 Primary assessment items analysis for intra-patient comparisons of avalglucosidase alfa to other ERT at individual patient level

For patients previously receiving **other ERT**, differences in mean of primary assessment items between **other ERT** treatment to avalglucosidase alfa treatment will be calculated and presented by a waterfall plot. Mean values and their CIs for each endpoint at each time point will also be plotted by grouped bar charts or line charts, depending on number of time points of data collection. Wilcoxon signed rank test will be performed to examine whether statistical difference between two treatment periods. Slopes of lines between two or more values of endpoints over time following treatment will be used to compare avalglucosidase alfa to **other ERT** to evaluate the

evolution of treatment outcomes with avalglucosidase alfa. Improvement, stabilization, and decline will be categorized based on the difference in outcomes during treatment with avalglucosidase alfa compared to **other ERT**. Cut-off points will be defined according to the distribution of data collected. Improvement, stabilization, or decline of CK, urinary Glc4/Hex4, QMFT and FVC% is dependent on both the actual magnitude of the slope change and the sample size. Generalized linear models will be performed for the association between primary assessment items and treatment (avalglucosidase alfa vs. avalglucosidase alfa) by considering repeated measurements for each patient. Multiple regression analyses will also take a range of covariates into account, including sociodemographic characteristics and factors pertaining to avalglucosidase alfa treatment.

4.4.1 Secondary assessment items analysis:

The main approach is a descriptive analysis, including spaghetti plots of the within-patient data over time during avalglucosidase treatment in treatment naïve patients and during other ERT and avalglucosidase alfa treatment in switch patients. Depending on the number of patients enrolled and amount of available data at the time of each report, exploratory statistical analyses may be performed. For all statistical testing in exploratory analyses, p-values < 0.05 will be considered as statistically significant.

The effectiveness analyses of secondary assessment items will be performed depending on the completeness of data. The data will be illustrated by line plots. Grouped bar charts will be used if the data are measured at less than three time points. Wilcoxon signed rank test will be used for comparing difference between each time points for endpoints measured biannually or annually (e.g., cardiac functions and 6-minute walk test). Bar charts or grouped bar charts will be plotted for description. However, if data are only measured at one time point, descriptive statistics will be presented to illustrate distribution of variables. A table of AEs will be generated by summarizing the event number and incidence of TEAE, IAR and Grade 1-4 AEs. The event number and incidence of each AE will also be graded by severity (Grade 1-4) and ranked by frequency and percentage of total analytic subjects in the table.

4.5 Handling of missing data

We will try every effort to communicate with physicians to follow up and complete the available data. Missing completely at random or missing at random is assumed for missing mechanism in the process of data collection. Complete case analyses will be performed based on endpoints without missing values. A direct likelihood approach to missing assessments with no further need for imputation is allowed. If missingness is related to some known factors (e.g., site-level, physician-level, and patient-level characteristics) or a large proportion of missing data is found (> 15%), sensitivity analyses will be performed by comparing results of complete case analyses to results with missing values imputed with mean values of total patients.

5. Data anonymization/de-identification

Patient-level data will be de-identified for presentation to offer increased protection for patient privacy through masking or generalization of direct and some indirect identifiers will be generated.

6. Report

Sanofi has planned to have a total of 2 reports for this study. There will be one interim report in 2024 Q4 (N=26 cumulatively) and one final report in 2026 Q4 (N=26 cumulatively).

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