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Survival of patients with chronic acid sphingomyelinase deficiency (ASMD) in the United States: A retrospective chart review study

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ABSTRACT

Background: Acid sphingomyelinase deficiency (ASMD), historically known as Niemann–Pick disease type A, A/B, and B, is a rare lysosomal storage pathology with multisystemic clinical manifestations. The aims of this study were to estimate the survival probability in patients in the United States with chronic ASMD (ASMD types B and A/B), and to describe the disease characteristics of these patients.

Methods: This observational retrospective study included medical chart records of patients with chronic ASMD with retrievable data abstracted by 69 participating physicians from 25 medical centers in the United States. Included patients had a date of ASMD diagnosis or first presentation to a physician for ASMD symptoms (whichever occurred first) between January 01, 1990, and February 28, 2021. Medical chart records were excluded if patients were diagnosed with ASMD type A. Eligible medical chart records were abstracted to collect demographic, medical and developmental history, and mortality data. Survival outcomes were analyzed using Kaplan–Meier survival analyses from birth until death.

Results: The overall study population ($N = 110$) included 69 patients with ASMD type B, nine with type A/B, and 32 with ASMD "non-type A" (ASMD subtype was unknown, but patients were confirmed as not having ASMD type A). The majority of patients were male with a median age at diagnosis of 3.8 years. Thirty-eight patients died during the study observation period, at a median age of 6.8 years. The median (95% confidence interval) survival age from birth was 21.3 (10.2; 60.4) years. At diagnosis or first presentation, 42.7% patients had ≥1 ASMD-related complication; splenic (30.0%) and hepatobiliary (20.9%) being the most common, and 40.9% required ≥1 medical visit due to complications.

Conclusion: Patients with chronic ASMD in the United States have poor survival and significant burden of illness.

1. Introduction

Acid sphingomyelinase deficiency (ASMD), historically known as Niemann-Pick disease types A, A/B, and B, is an under-recognized, rare, debilitating lysosomal storage disease caused by autosomal recessive pathogenic variants in the *sphingomyelin phosphodiesterase 1* gene that encodes the enzyme acid sphingomyelinase [1–3]. ASMD is pan-ethnic and has an estimated birth prevalence of 0.4 to 0.6 cases per 100,000

Abbreviations: ASMD, acid sphingomyelinase deficiency; CI, confidence interval; ER, emergency room; IQR, interquartile range; NR, not reachable; SD, standard deviation.

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live births, affecting both sexes equally [4,5]. The clinical spectrum of ASMD is broadly divided into three types: type A (infantile neurovisceral ASMD), and two chronic forms, type B (chronic visceral ASMD), and the more recently described intermediate form type A/B (chronic neurovisceral ASMD) [3,5,6].

The diagnosis of ASMD is often delayed due to overlapping symptoms with other chronic conditions [7]. In addition, the differentiation between chronic ASMD types is difficult because genotype/phenotype correlations are not established for the majority of known pathogenic variants [7]. Awareness of the ASMD type A/B phenotype is also limited because ASMD was historically categorized as either Niemann-Pick type A or type B, thus establishing type based on presentation can also be complex.

Patients with ASMD type A experience disease onset in early infancy and have significant neurological manifestations, with death occurring by 3 years of age [6,8–10]. Patients with ASMD type A/B have an onset between infancy and childhood, and those with ASMD type B experience onset anytime from infancy to adulthood [1,5,6]. In cases of chronic ASMD (types B and A/B), common systemic clinical manifestations include organomegaly, interstitial lung disease and associated pulmonary complications, liver dysfunction, thrombocytopenia with associated bleeding episodes, dyslipidemia with increased risk of coronary artery disease, and skeletal abnormalities [11,12]. This substantial morbidity is associated with increased healthcare resource use, with a recent analysis observing that patients with ASMD type B had a high use of ASMD-related healthcare services (including inpatient and outpatient visits) and medications [14]. This high level of resource use is supported by recent management guidelines and monitoring experience, which suggest regular follow-ups should be conducted with treated and untreated patients [7,15].

Premature death due to complications, including respiratory and liver failure, is often reported in patients with chronic ASMD [13,19]. In a review of published case studies and new case reports, respiratory disease and liver disease were reported as the leading causes of death in patients with ASMD type B, accounting for 30.9% and 29.1% of deaths, respectively [13,20]. For patients with ASMD type A/B, respiratory disease (23.1%), neurodegeneration (23.1%), and liver disease (19.2%) were the primary causes of death [13]. A previous natural history study of 103 patients with ASMD type B in the United States, reported 18 deaths during the study and a median (range) age at death of 17 (2–72) years, with the majority of deaths occurring in patients aged <21 years [12].

In 2022, olipudase alfa (Xenpozyme®; Sanofi), a recombinant human acid sphingomyelinase, was approved as the first disease-specific therapy for the treatment of non-central nervous system manifestations of ASMD in adult and pediatric patients in the United States, Europe, Japan, and other countries [16–18]. Prior to this approval, ASMD management was restricted to supportive care to control symptoms [3].

Conducting retrospective studies that use real-world data from medical records may provide insights into the clinical manifestations and survival probability of this complex disease. Using real-world data from medical records, the primary objective of this study was to estimate the cumulative survival probability in patients with chronic ASMD. The secondary objective was to describe the characteristics of patients with chronic ASMD, including disease characteristics, ASMD-related complications, and healthcare resource use.

2. Materials and methods

2.1. Study design

This was an observational, multicenter, retrospective cohort study. Data were obtained from medical chart records abstracted by 69 participating physicians from 25 medical centers in the United States. Recruited physicians were board-certified and had been in practice between 3 and 40 years. To participate in the study, physicians were required to have treated or managed at least one patient with chronic ASMD, diagnosed by enzymatic or genetic testing, in the previous 3 years. Physicians with the following specialties were included: geneticists, metabolic disease specialists, pediatricians/primary care specialists, hematologists, neurologists, pulmonologists, internal medicine specialists, general practitioners, hepatologists, endocrinologists, and gastroenterologists.

Patients with chronic ASMD alive or deceased between January 1st, 1990 and February 28th, 2021 were eligible for inclusion. Patients diagnosed with ASMD type A (based on identified genotype), those who had participated in a previous Sanofi-sponsored study, or those with no retrievable information from the medical record (data not recorded or not correctly recorded), were excluded. When genotype information was missing, these medical charts were abstracted irrespective of ASMD type, due to the well understood difficulty in accurately diagnosing different ASMD types. A medical data review was then conducted by the sponsor to evaluate records with missing genotype data, in order to exclude patients with ASMD type A (categorized as patients with age of death ≤3 years [9]). At the time of the study, awareness of the ASMD type A/B phenotype was limited, and the introduction of this terminology in the nomenclature may have pre-dated any diagnosis information included in medical records. Therefore, due to the retrospective nature of the study, records assigned as ASMD type A/B also underwent medical review by the sponsor to ensure correct categorization.

2.2. Data collection

Data were extracted retrospectively by physicians from patient medical records during the study observation period (between January 1, 1990, and February 28, 2021), defined as the time from diagnosis or first clinical presentation date (whichever was earlier) to patients' date of last follow-up, end of study period, or death (whichever occurred first). The first presentation date was defined as the date the patient first presented to the responding physician for ASMD symptoms.

Demographic characteristics, medical history (ASMD type, age at diagnosis or first presentation), pre-existing/known medical conditions in addition to ASMD, relevant ASMD complications, healthcare resource use relating to complications, and mortality data (age at death and cause of death) were extracted from eligible medical chart records.

Medical conditions in addition to ASMD and ASMD-related complications included: myocardial infarction; cerebrovascular disease; heart valve abnormality; hemorrhagic diathesis or abnormal bleeding; hematological diseases (e.g., thrombocytopenia, anemia, etc.); lung diseases (e.g., interstitial lung disease, etc.); asthma; tobacco use; hepatitis C; chronic liver dysfunction; congestive heart failure; myalgia; other (to be specified based on data); liver complications (hepatomegaly, cirrhosis of the liver, portal hypertension, ascites, esophageal varices, other); splenic complications (splenomegaly, splenectomy, hypersplenism, splenic infarction, rupture of the spleen, anemia, increased bleeding, other), cardiovascular complications (ventricular hypertrophy graded, heart valve disease, pulmonary hypertension, atherosclerosis, arrhythmia, hypertension, myocardial infarction, cerebrovascular accident, other); lower respiratory tract infections (clinical features of interstitial lung disease, alveolar infiltrates, respiratory distress, infection of the lower airway, other); surgery complications; and external bleeding episodes (bleeding gums, hematemesis, rectal bleeding, prolonged bleeding time, hemangioma, increased tendency to bruise, petechiae, other).

Healthcare resource use (due to ASMD-related complications) included: all-cause hospitalizations, inpatient stays, outpatient stays, emergency room (ER) visits, and office visits.

2.3. Statistical analyses

Demographic characteristics and medical and development history were recorded at date of diagnosis or first presentation and date of last

follow-up or death, and were characterized using descriptive statistics. Complications and healthcare resource use could be categorized as "unknown" in the medical chart, defined as an event declared at diagnosis, first presentation, or last follow up, but without any associated date. The proportion of patients with ASMD complications and healthcare resource use declared as "unknown", were combined with those patients who had an exact date associated with the event.

To address the primary objective of this study, a time-to-event analysis estimating the cumulative probability of survival from birth was performed using the Kaplan-Meier method. The median overall survival, defined as the time from birth until death due to any cause (event) or last follow-up date, with two-sided 95% confidence intervals (CIs) was calculated. Data from surviving patients were censored at the date of the last follow-up (end of the observation period), as the event (death) could not be observed after this time. From this age onwards, the patient was dropped from the number of patients at risk of dying for survival computation to avoid overestimating survival. Cumulative survival probabilities, i.e., the proportion of patients surviving (or remaining event free) at the end of the study period, were calculated from birth. Survival outcomes were described in the overall study population and according to ASMD type (type B and type A/B).

Life expectancy at birth in patients with chronic ASMD and people in the general United States population was computed post hoc as the area under the survival curve using Microsoft Excel (version 2208). Each age-related life expectancy was estimated as the area under the curve, being left bounded by the current age y-axis parallel. Life expectancy data in the general population were derived from 2018 mortality data from the National Center for Health Statistics, National Vital Statistics System [21]. All other data analyses were conducted using SAS statistics software version 9.4 (SAS Institute Inc., Cary, NC, USA); all figures were generated with R software version 4.1.3. No imputation was performed for missing data.

2.4. Ethical approvals

This study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice, and applicable regulatory requirements. This study was conducted in accordance with the regulations of the United States Food & Drug Administration as described in 21 CFR 50 and 56, applicable laws and the institutional review board/ethics committee requirements.

3. Results

3.1. Study participants

Among the 127 medical charts identified, 69 patients (62.7%) with ASMD type B and nine patients (8.2%) with ASMD type A/B were identified (Fig. 1). An additional 32 patients (29.1%) did not have available clinical and genotype data, and therefore could not be confirmed as having chronic ASMD. However, these patients were confirmed as not having ASMD type A according to clinical presentation and patient profile and were thus described as having ASMD "non-type A". Therefore, the overall study population included 110 patients with chronic ASMD.

Demographics and characteristics of the study population are presented in Table 1. The majority of patients were male (63.6%) and the median age at diagnosis or first presentation was 3.8 or 3.9 years, respectively. The median (interquartile range [IQR]) follow-up duration from diagnosis or first presentation of ASMD was 4.0 (1.6–7.6) years overall. At diagnosis or first presentation, the median (IQR) weight of the overall study population was 19.7 (11.3 to 44.9) kg, which increased to 28.1 (16.3 to 63.5) kg at death or last follow-up (Table 1); however, the age range was broad, and weight was not reported according to age category.

3.2. Mortality characteristics

During the observation period, 38 (34.5%) patients died, including 34 of 98 (34.7%) pediatric patients and 4 of 12 (33.3%) adult patients (Table 2). Median (IQR) age at death and last follow-up for the overall study population were 6.8 (5.0–18.5) years and 9.8 (5.0–20.0) years, respectively. The cause of death was mostly unknown (86.8%), while respiratory disease (2.6%), multi-organ failure (5.3%), and severe progressive neurodegeneration (5.3%) were noted in a few cases (Table 2).

3.3. Overall survival

The median (95% CI) survival for the overall study population was 21.30 (10.15; 60.38) years from birth (Fig. 2A). There was heavy censoring of the study population, with approximately two-thirds of the sample being censored by age 30 years (**Supplementary Fig. 1**). A major reason for the heavy censoring was that many patients were very young at study completion (only four of the 110 patients were born prior to 1980). Of the 72 censored patients, 65 (90.3%) had a follow-up appointment within 2 years prior to study completion.

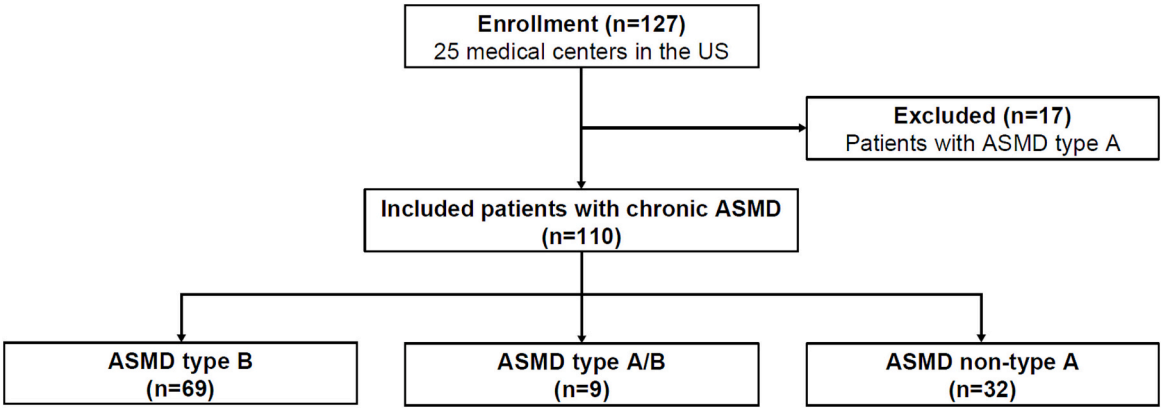

Fig. 1. Disposition of study participants with ASMD.
ASMD non-type A was defined as patients for whom subtype could not be determined due to an absence of genotype data, but who were confirmed as not having ASMD type A according to clinical presentation and patient profile.
ASMD, acid sphingomyelinase deficiency.

Table 1
Demographics and characteristics of patients according to ASMD type.

	All patients (n = 110)	ASMD type		
		Type B (*n* = 69)	Type A/B (*n* = 9)	Non-type A (*n* = 32)
Age at diagnosis (years)				
Mean (SD)	8.29 (10.96)	8 (9.31)	11.90 (23.56)	7.91 (9.19)
Median (IQR)	3.75 (1.74; 11.98)	3.71 (1.71; 11.98)	3.79 (3.04; 4.71)	3.75 (1.93; 13.84)
Range	0; 74.22	0; 52.62	0.60; 74.22	0; 44.13
Age at first presentation (years)				
Mean (SD)	8.33 (11.56)	7.93 (9.36)	11.27 (23.63)	8.38 (11.41)
Median (IQR)	3.89 (1.30; 10.96)	3.33 (1.50; 10.96)	3.71 (2.17; 4.85)	4.42 (1.25; 12.38)
Range	0; 73.97	0; 52.62	0.15; 73.97	0.01; 59.88
Number of patients at diagnosis or first presentation categorized by age, n (%)				
<18 years	98 (89.1)	60 (87.0)	8 (88.9)	30 (93.8)
≥18 years	12 (10.9)	9 (13.0)	1 (11.1)	2 (6.3)
Sex, n (%)				
Female	40 (36.4)	20 (29.0)	5 (55.6)	15 (46.9)
Male	70 (63.6)	49 (71.0)	4 (44.4)	17 (53.1)
Geographic region*, n (%)				
East	26 (23.6)	15 (21.7)	6 (66.7)	5 (15.6)
West	48 (43.6)	32 (46.4)	1 (11.1)	15 (46.9)
North	11 (10.0)	7 (10.1)	1 (11.1)	3 (9.4)
South	25 (22.7)	15 (21.7)	1 (11.1)	9 (28.1)
Family history of ASMD, n (%)				
Yes	20 (18.2)	15 (21.7)	3 (33.3)	2 (6.3)
Weight (all ages) at diagnosis or first presentation, kg				
Mean (SD)	28.44 (21.84)	29.10 (22.33)	21.92 (19.74)	28.84 (21.64)
Median (IQR)	19.73 (11.34; 44.90)	19.50 (11.34; 47.62)	12.70 (10.88; 22.68)	21.54 (12.02; 37.41)
Weight (all ages) at death or last follow-up, kg				
Mean (SD)	39.93 (26.45)	38.74 (26.30)	34.16 (24.03)	44.12 (27.62)
Median (IQR)	28.12 (16.33; 63.49)	27.66 (14.97; 63.49)	19.50 (14.97; 58.05)	46.26 (19.27; 66.67)
Past surgical history of splenectomy, n (%)				
Yes	12 (10.9)	10 (14.5)	1 (11.1)	1 (3.1)
Type of splenectomy†, n (%)				
Total	7 (58.3)	6 (60.0)	1 (100.0)	0
Partial	5 (41.7)	4 (40.0)	0	1 (100.0)

ASMD, acid sphingomyelinase deficiency; IQR, interquartile range; SD, standard deviation.

* Region within the United States which characterize the location of the practitioner.

† Types of splenectomy among patients with a past surgical history of splenectomy.

3.4. Life expectancy

In 2018, life expectancy at birth in the United States general population was approximately 79 years (Fig. 3) [22]. In contrast, life expectancy at birth of the overall study population (*n* = 110) was approximately 37 years.

3.5. Medical conditions in addition to ASMD and ASMD-related complications

At diagnosis or first presentation, 40.9% of the overall study population had at least one medical condition in addition to ASMD described in their medical record, with chronic liver dysfunction (15.5%), lung

Table 2
Survival characteristics of patients according to ASMD type.*

Characteristic	All patients (N = 110)	ASMD type		
		Type B (n = 69)	Type A/B (n = 9)	Non-type A (n = 32)
Follow-up duration from diagnosis or first presentation, years				
Mean (SD)	5.75 (5.89)	4.89 (5.47)	4.93 (5.5)	7.85 (6.5)
Median (IQR)	3.98 (1.54; 7.55)	3.2 (1.04; 7.23)	2.28 (0.85; 11.08)	5.68 (3.61; 10.37)
Range	0; 28.32	0; 28.32	0.14; 12.93	0.52; 21.84
Death, N (%)				
Yes	38 (34.5)	23 (33.3)	3 (33.3)	12 (37.5)
Age at last follow up, years				
Mean (SD)	13.33 (12.23)	12.24 (10.61)	16.03 (22.87)	14.91 (11.7)
Median (IQR)	9.77 (4.97; 19.96)	8.8 (3.96; 20.01)	5.29 (3.52; 16.41)	12.14 (6.12; 20.02)
Range	0.35; 74.38	0.35; 54.42	1.85; 74.38	4.16; 60.38
Weight (all ages) in patients surviving at last follow-up, kg				
n	72	46	6	20
Mean (SD)	41.97 (26.58)	38.44 (25.64)	32.05 (24.85)	53.06 (27.02)
Median (IQR)	40.59 (16.55; 65.53)	27.66 (14.51; 62.59)	17.69 (14.97; 58.05)	55.56 (22.22; 73.70)
Time from diagnosis or first presentation to death, years				
Mean (SD)	5.41 (4.61)	4.58 (3.56)	4.88 (6.61)	7.14 (5.78)
Median (IQR)	4.28 (2.15; 7.35)	3.7 (1.17; 7.35)	1.74 (0.42; 12.48)	4.48 (3.98; 7.36)
Range	0.42; 21.16	0.46; 11.65	0.42; 12.48	3.08; 21.16
Age at death, years				
Mean (SD)	12.98 (14.95)	10.54 (8.26)	30.7 (38.47)	13.22 (15.75)
Median (IQR)	6.83 (4.97; 18.49)	6.65 (4.05; 19.79)	15.88 (1.85; 74.38)	6.83 (5.66; 14.32)
Range	0.61; 74.38	0.61; 27.01	1.85; 74.38	4.97; 60.38
<18 years old, n (%)	28 (73.7)	17 (73.9)	2 (66.7)	9 (75.0)
≥18 years old, n (%)	10 (26.3)	6 (26.1)	1 (33.3)	3 (25.0)
Cause of death, n (%)				
Respiratory disease	1 (2.6)	0	0	1 (8.3)
Multi-organ failure	2 (5.3)	1 (4.4)	1 (33.3)	0
Severe progressive neurodegeneration	2 (5.3)	1 (4.4)	0	1 (8.3)
Unknown	33 (86.8)	21 (91.3)	2 (66.7)	10 (83.3)
Death related to ASMD, n (%)				
No	1 (2.6)	1 (4.4)	0	0
Yes	2 (5.3)	1 (4.4)	1 (33.3)	0
Unknown	35 (92.1)	21 (91.3)	2 (66.7)	12 (100.0)
Overall cumulative survival probability (95% CI) from birth				
1-year survival probability	98.2 (92.9; 99.5)	97.1 (88.7; 99.3)	100 (100.0; 100.0)	100 (100.0; 100.0)
5-year survival probability	90.1 (82.4; 94.6)	87 (75.6; 93.3)	88.9 (43.3; 98.4)	96.8 (79.2; 99.5)
10-year survival probability	75.4 (65.0; 83.2)	76.7 (63.0; 85.9)	88.9 (43.3; 98.4)	71.7 (51.1; 84.8)

ASMD, acid sphingomyelinase deficiency; CI, confidence interval; IQR, interquartile range; NR, not reachable; SD, standard deviation.

* 95% CI refer to 25th and 75th percentile.

diseases (14.6%), myalgia (11.8%), asthma (10.0%), and hemorrhagic diathesis or abnormal bleeding (8.2%) being the most common (Table 3). At death or last follow-up, 60.0% of patients had at least one medical condition in addition to ASMD, the most common of which were chronic liver dysfunction (28.2% of patients), lung diseases (24.6%), and myalgia (23.6%; **Supplementary Table 1**).

At least one ASMD complication was described in the medical records of 42.7% of patients at diagnosis or first presentation (Fig. 4), with splenic (30.0%) and hepatobiliary (20.9%) being the most common. The proportion of patients with ASMD type B with at least one complication (46.4%) was comparable with the overall study population. At death or last follow-up, 51.8% of patients in the overall study population had at least one ASMD complication, with splenic (36.4%) and hepatobiliary (26.4%) again being the most common (**Supplementary Table 2**). The median (IQR) time from diagnosis or first presentation to first

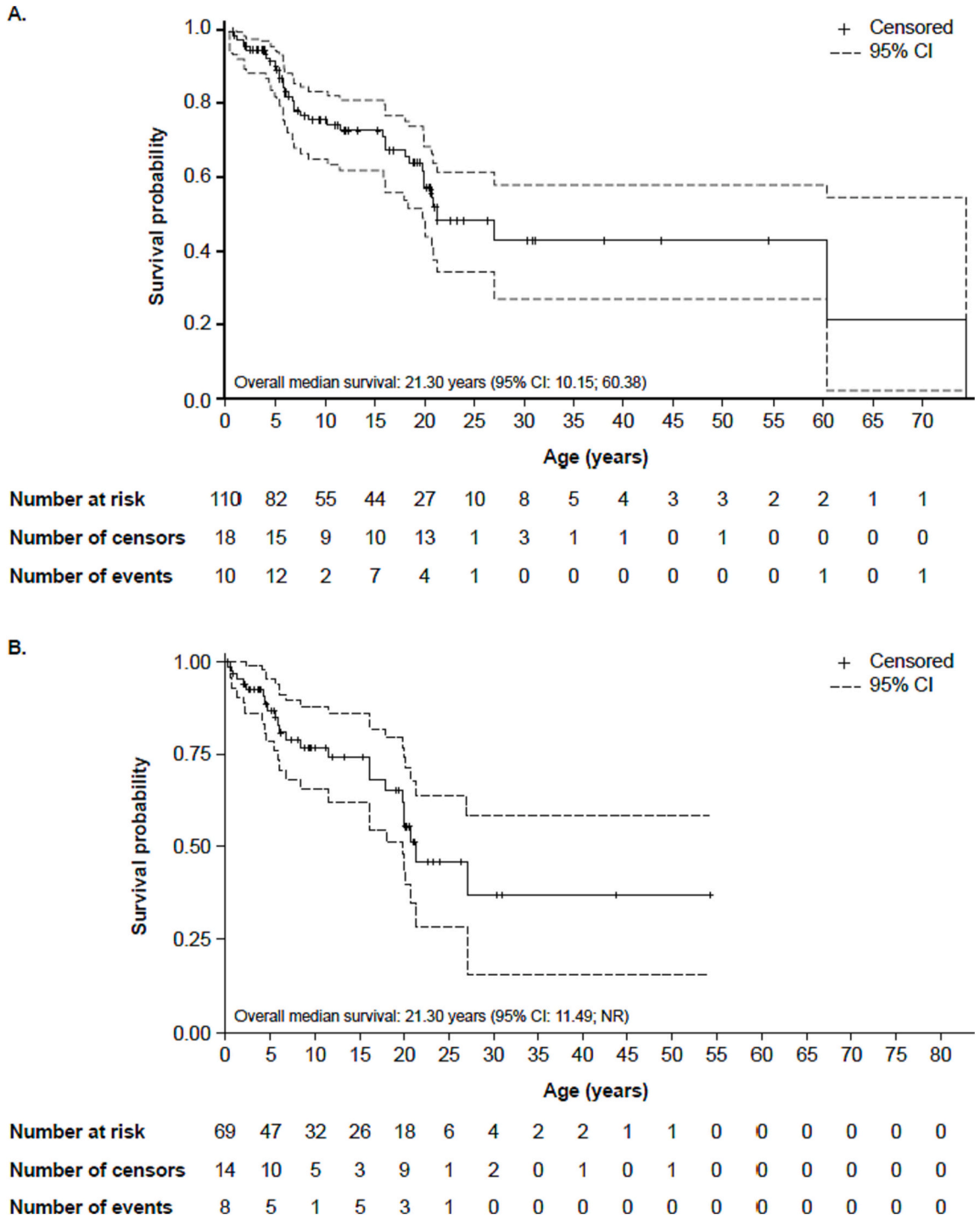

Fig. 2. Kaplan–Meier survival curve from birth in patients with A) chronic ASMD ($N = 110$) and B) ASMD type B ($N = 69$).
ASMD, acid sphingomyelinase deficiency; CI, confidence interval; NR, not reachable. In patients with ASMD type B ($n = 69$), median (95% CI) overall survival age was 21.30 (11.49; not reachable [NR]) years from birth (Fig. 2B). An equivalent survival analysis for patients with ASMD type A/B was not considered feasible due to the small sample size.

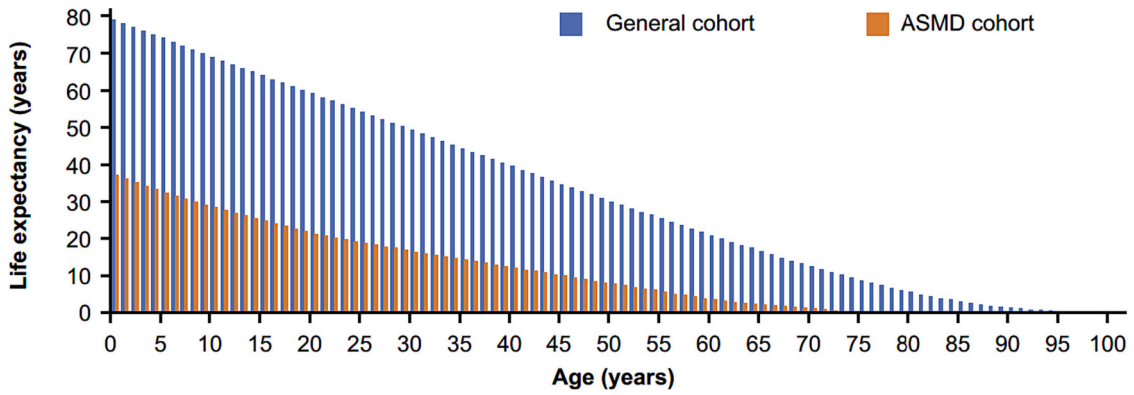

Fig. 3. Life expectancy of patients with chronic ASMD ($N = 110$) and general population in the United States.
Source for general population data: National Center for Health Statistics (NCHS) National Vital Statistics System, Mortality data 2018. ASMD, acid sphingomyelinase deficiency.

Table 3
Medical conditions in addition to ASMD at diagnosis or first presentation and according to ASMD type.

n (%)	All patients ($N = 110$)	ASMD type		
		Type B ($n = 69$)	Type A/B ($n = 9$)	Non-type A ($n = 32$)
Any medical conditions in addition to ASMD	45 (40.9)	34 (49.3)	2 (22.2)	9 (28.1)
Myocardial infarction	1 (0.9)	1 (1.5)	0	0
Cerebrovascular accident	1 (0.9)	0	0	1 (3.1)
Cardiac valvular abnormality	6 (5.5)	4 (5.8)	0	2 (6.3)
Hemorrhagic diathesis or abnormal bleeding	9 (8.2)	8 (11.6)	0	1 (3.1)
Hematologic malignancies*	8 (7.3)	5 (7.3)	0	3 (9.4)
Lung diseases	16 (14.6)	11 (15.9)	1 (11.1)	4 (12.5)
Asthma	11 (10.0)	8 (11.6)	1 (11.1)	2 (6.3)
Tobacco use	4 (3.6)	3 (4.4)	0	1 (3.1)
Hepatitis C	1 (0.91)	0	0	1 (3.1)
Chronic liver dysfunction	17 (15.5)	13 (18.8)	1 (11.1)	3 (9.4)
Congestive heart failure	4 (3.6)	3 (4.4)	0	1 (3.1)
Myalgia	13 (11.8)	7 (10.1)	1 (11.1)	5 (15.6)
Other (unspecified)	1 (0.9)	0	1 (11.1)	0

Medical conditions in addition to ASMD at diagnosis or first presentation were defined as any record of medical condition before or at first presentation or diagnosis dates. Patients could declare multiple medical conditions (medical conditions were not mutually exclusive).
ASMD, acid sphingomyelinase deficiency.
* Including thrombocytopenia, anemia, etc.

complication was 0.14 (0; 0.5) years, with a median (IQR) age at first complication of 4.1 (1.6; 7.8) years (**Supplementary Table 2**).

3.6. Healthcare resource use relating to ASMD complications

Overall, 40.9% of patients at diagnosis or first presentation and 39.1% of patients at last follow-up had a record of at least one type of medical visit (including inpatient, outpatient, or ER visits) due to ASMD-related complications (Fig. 5 and **Supplementary Table 3**). The proportion of patients with at least one medical visit was lowest for ASMD non-type A (25.0%) compared with ASMD type B (46.4%) and type A/B (55.6%) (Fig. 5). The most common medical visits by patients at diagnosis or first presentation was office visits (39.1%), followed by outpatient visits (36.4%) and ER visits (20.0%) (Fig. 5); these were also the most common visits at last follow-up (**Supplementary Table 4**). Overall, hepatobiliary complications were the most common reason for medical visits, with 30.9% of patients at diagnosis or first presentation and 27.3% at death or last follow-up experiencing at least one such visit due to this particular complication (**Supplementary Tables 3 and 4**).

4. Discussion

The results from this retrospective chart review revealed a high mortality rate and substantial and heterogenous burden of illness among patients with chronic ASMD in the United States. Characteristics of patients included in the study were comparable with previous reports of patients with ASMD type B; the mean age at diagnosis (8.3 years) was similar to the mean age reported by McGovern et al. (2008) in a prospective cross-sectional survey study of patients with ASMD type B (9.8 years) [1]. Of the 38 patients who died during the study, 73.7% were aged <18 years at death. These results reinforce previous findings by McGovern et al. (2013) who reported that two thirds of deaths in patients with ASMD type B occurred in those aged 21 years and younger [12]. The median age of death (17 years) reported by McGovern et al. (2013) was higher than that observed in the current study (6.8 years) [12]. However, survival in pediatric patients can be estimated in McGovern et al. (2013) from the Kaplan–Meier curve as approximately 21 years, comparable to the median survival age from birth of 21.3 years reported here [12]. Median survival age in the McGovern et al. (2021) study was estimated much later than the present study at 57 years (calculated from Kaplan–Meier curve), reflecting the older age distribution in the study, in which approximately half of patients were adults at baseline and nearly all at final visit [19]. However, the comparison of point estimates of median survival across studies should be done with caution, considering that the ultra-rareness of ASMD limits the sample sizes and widens the confidence intervals of the survival estimates.

The cause of death was unknown in the majority of patients who died during the current study observation period; however, five deaths could be attributed to respiratory disease, multi-organ failure, or severe progressive neurodegeneration. These reported causes of death are in line with previously published causes of mortality in chronic ASMD, with respiratory disease a well-established cause of death in this patient population and neurodegeneration a known cause of death in patients with ASMD type A/B [13,19,20].

Overall, chronic liver dysfunction and lung diseases were the most common medical conditions in addition to ASMD reported at diagnosis or first presentation, followed by myalgia, asthma, and hemorrhagic diathesis or abnormal bleeding. These results were generally consistent with a natural history study of ASMD type B by McGovern et al. (2013), which reported liver disease, pulmonary disease, and bleeding disorders as major morbidities [12]. McGovern et al. (2013) also reported that eight patients had neurological findings (including motor delays and ataxia) and categorized them as having variant Niemann–Pick type B (ASMD type A/B) [12]. In the present study, only one patient had a record of cerebrovascular accident, although nine patients with ASMD

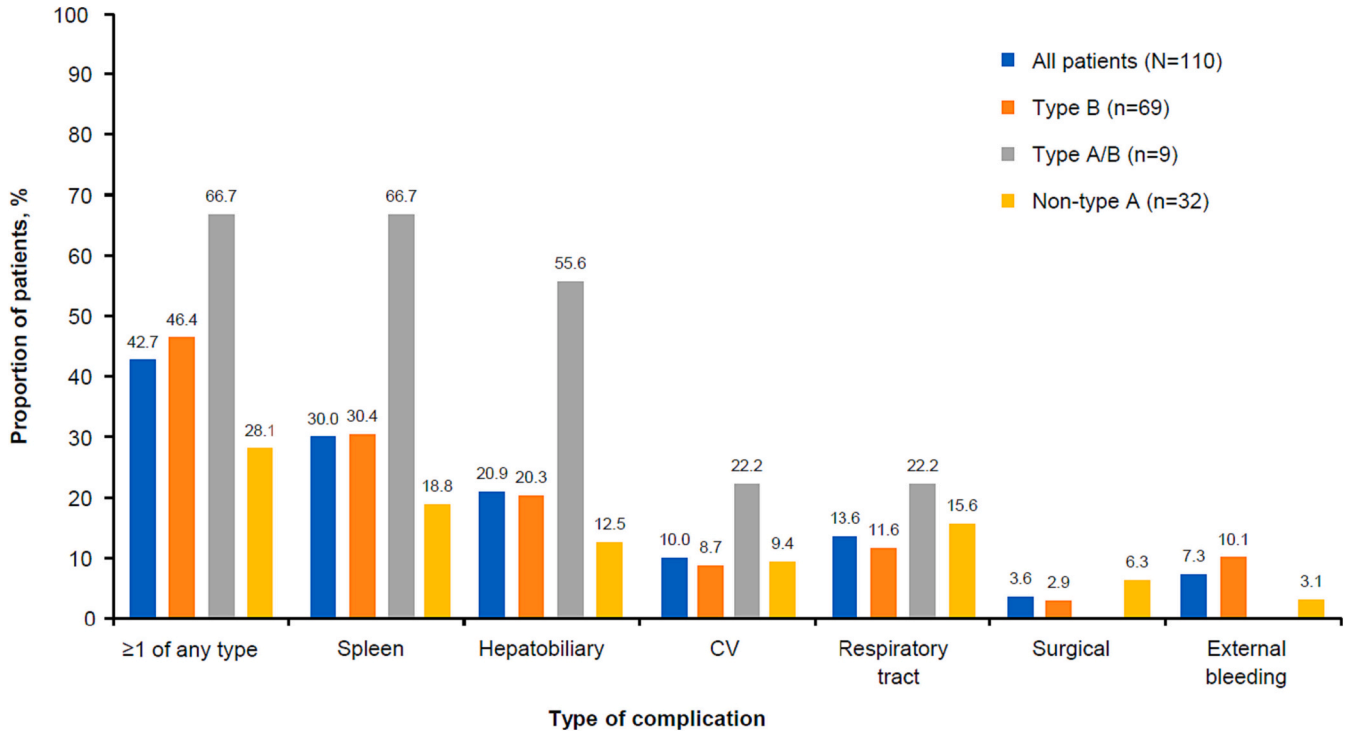

Fig. 4. Proportion of patients with at least one ASMD-related complication at diagnosis or first presentation according to ASMD type.
The proportion of patients with each complication included patients with and without an exact date associated with the complication in their medical chart. Patients were included with at least one complication recorded before diagnosis or first presentation, whichever is earlier. Patients could declare multiple complications (complications were not mutually exclusive).
ASMD, acid sphingomyelinase deficiency.

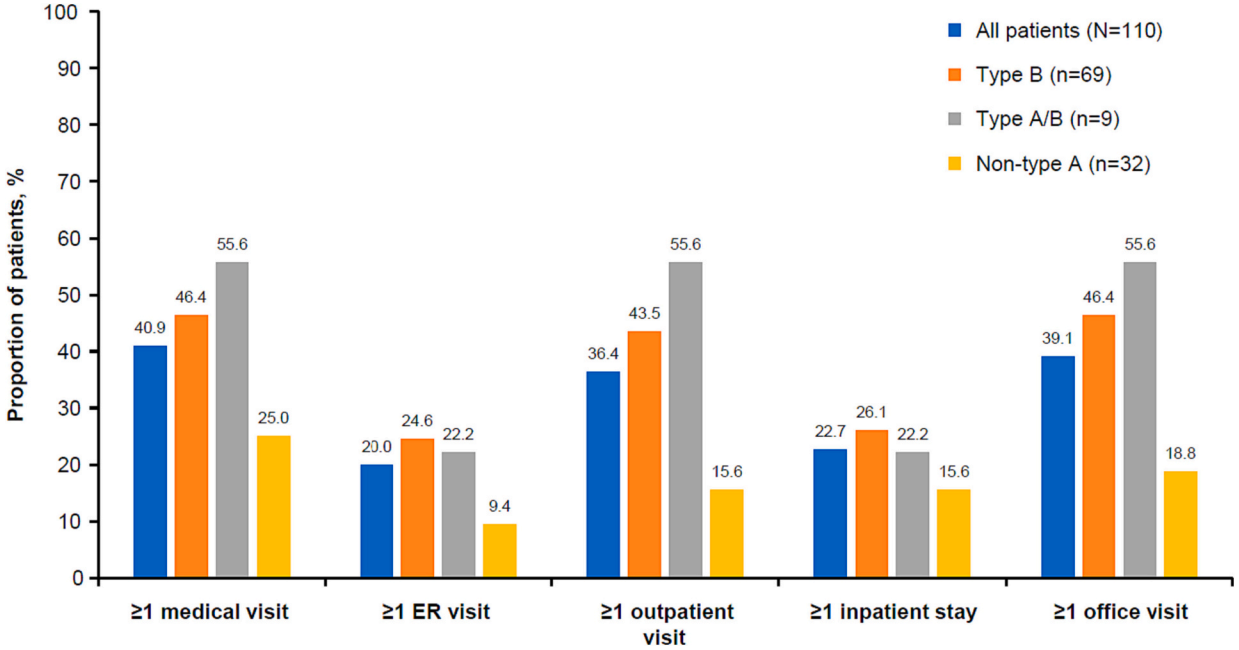

Fig. 5. Proportion of patients with at least one medical visit (by type) at diagnosis or first presentation according to ASMD type.
Medical visits included inpatient, outpatient, or ER visits. The proportion of patients with each medical visit included patients with and without an exact date associated with the visit in their medical chart. Inpatient stay was defined by at least 1 night at hospital (length of stay at hospital >1 stay). ASMD, acid sphingomyelinase deficiency; ER, emergency room.

type A/B were included. Splenic and hepatobiliary symptoms (recorded as complications in the present study and including splenomegaly and hepatomegaly, respectively) were the most common complications at diagnosis or first presentation in patients with ASMD type B (30.0% and 20.9%, respectively). This was in line with the prospective cross-sectional survey study by McGovern et al. (2008) that described

splenomegaly and hepatomegaly, along with respiratory disease, excessive bleeding/bruising, and thrombocytopenia, as presenting signs and symptoms in patients ASMD type B [1].

Over one-third of patients with chronic ASMD had attended at least one outpatient visit and at least one office visit due to ASMD-related complications at diagnosis or first presentation, with similar proportions at final follow-up. These results support existing research demonstrating that there is a high level of healthcare resource use (including hospitalizations, surgeries, medication use, and outpatient visits) associated with ASMD prior to the availability of olipudase alfa [14,23], and highlights the need for regular clinical assessment [5].

4.1. Limitations

Limitations of the study included the exclusion of patients who had participated in previous Sanofi-sponsored studies to prevent overlap of cohorts, including the recent prospective longitudinal study in patients with chronic ASMD by McGovern et al. (2021) [19], thereby reducing the number of medical records available to include in the study. However, to our knowledge, this is the largest chronic ASMD cohort analyzed for survival. Only nine patients with ASMD type A/B were included in the study, and as such survival analyses by type were difficult to interpret as death outcomes were too few. In addition, the exclusion of patients with ASMD type A was based on age alone (death at $\leq$3 years) and the overall clinical presentation was not considered, due to the limited variables of interest in the data collection. However, the overall survival for the study population, which included patients with ASMD non-type A, was the same as for patients with confirmed ASMD type B, thus, patients with ASMD non-type were included in the study.

The proportions of patients with splenic and hepatic complications and the proportion of patients with medical visits, was lower than expected considering the high morbidity and mortality in the population. However, only data on healthcare resource use relating to ASMD complications were collected in the study, rather than overall healthcare resource use, therefore limiting the analysis. Moreover, data were collected by medical centers, therefore, medical visits may have been underreported if outpatient consultations occurred outside of the center. In addition, these limitations may have been due to incomplete data for extraction in the medical records, despite patients likely presenting with these manifestations. Another limitation was that data on neurological manifestations were also not collected as pre-specified medical conditions in addition to ASMD or complications, despite patients with ASMD type A/B being included in the study. The severity grading of complications associated with clinical visits was collected, but there were insufficient data for meaningful interpretation.

The retrospective study design relies on the accuracy of medical records; therefore, in the absence of a disease-specific treatment for ASMD at the time of the study, some patients may not have been motivated to undergo routine clinical examination or were too ill for follow-up visits, resulting in sparse data. Breaks in medical records as a result of switching physicians or receiving referrals were also likely; hence, the full medical histories of some patients may not have been available, thereby limiting the accuracy of the records. At the time of the study, there were no clinical guidelines for the monitoring or managing of patients with chronic ASMD, therefore, some examinations and assessments may not have been regularly performed and reported, as currently recommended in recent guidelines [7,9]. The beginning of the observation period was the time from diagnosis or the first presentation to the responding physician, which could be different from the time of symptom onset and, therefore, may not reflect true disease presentation. Given the rarity of ASMD, this research may have captured an overlap of patients while visiting different specialties, based on different parts of their journey.

4.2. Conclusions

The results from this study demonstrate a significant and heterogenous burden of illness with a high mortality rate in patients from the United States with chronic ASMD. Morbidity associated with splenic, hepatobiliary, and lung disease complications, as well as a high rate of medical visits, was reported. The median survival age at birth was 21.30 years for patients with chronic ASMD and life expectancy was around half of that in the general United States population, demonstrating the substantial life-shortening impact of this disease. The results of this study highlight the need for a disease-modifying treatment for patients with chronic ASMD in the United States.

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Author contributions

- **RPJ, AA, SD, and BS** made substantial contributions to study conception and design.
- **RPJ, AA, SD, and BS** made substantial contributions to the acquisition of data
- **RPJ, AK, AC, TM, SG,** and **GG** made substantial contributions to analysis of data.
- **RPJ, AK, AC, TM**, **SG, LP**, and **GG** made substantial contributions to the interpretation of data.

All authors were involved in drafting the work or revising it critically for important intellectual content, and in final approval of the version to be published. All authors have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Previous presentations

These data were presented in part at the 2022 NORD Rare Diseases and Orphan Products Breakthrough Summit, October 17–182022, and at the 19th Annual WORLDSymposium, February 22–26, 2023

CRediT authorship contribution statement

Ruth Pulikottil-Jacob: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. **Sumudu Dehipawala:** Conceptualization, Data curation, Investigation, Writing – original draft, Writing – review & editing. **Brittany Smith:** Writing – original draft, Writing – review & editing, Conceptualization, Data curation. **Amod Athavale:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **Gaelle Gusto:** Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Aastha Chandak:** Investigation, Writing – original draft, Writing – review & editing. **Artak Khachatryan:** Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Tamar Banon:** Investigation, Writing – original draft, Writing – review & editing. **Marie Fournier:** Writing – original draft, Writing – review & editing, Investigation. **Sophie Guillonneau:** Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Laurence Pollissard:** Investigation, Writing – original draft, Writing – review & editing. **Maria Veronica Munoz-Rojas:** Validation, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

MVMR, MF, RPJ, SG, and **LP** are employees and shareholders of Sanofi.

SD, BS, and **AA** are employees of Trinity Life Sciences.

GG, AC, AK, and **TB** are employees of Certara, which received funding from Sanofi for this research.

Data availability

Qualified researchers may request access to patient level data and related study documents including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications. Patient level data will be anonymized and study documents will be redacted to protect the privacy of our trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at: https://www.vivli.org/.

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Appendix A. Supplementary data

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