Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2025-B-083 Olipudase alfa

Stand: Mai 2025

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Olipudase alfa
[Behandlung eines Mangels an saurer Sphingomyelinase (ASMD)]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	nicht angezeigt
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	*Olipudase alfa vom 16. März 2023*
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Olipudase alfa A16AB25 Xenpozyme®	**<u>Anwendungsgebiet laut Zulassung</u>** Xenpozyme ist als Enzymersatztherapie zur Behandlung von Manifestationen eines Mangels an saurer Sphingomyelinase (ASMD) außerhalb des zentralen Nervensystems (ZNS) bei Kindern, Jugendlichen und Erwachsenen mit Typ A/B oder Typ B indiziert.
Für das vorliegende Anwendungsgebiet sind neben Olipudase alfa keine weiteren Arzneimittel zugelassen.	

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie

Vorgang: 2025-B-083 (Beratung nach § 35a SGB V) Olipudase alfa

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	17. April 2025

Inhaltsverzeichnis

Abkürzungsverzeichnis

ASMD	Acid Sphingomyelinase Deficiency
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
ECRI	Emergency Care Research Institute
G-BA	Gemeinsamer Bundesausschuss
GDG	Guidelines Development Group
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
INPDA	International Niemann–Pick Disease Alliance
KI	Konfidenzintervall
LoE	Level of Evidence
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Zur Behandlung von Manifestationen eines Mangels an saurer Sphingomyelinase (ASMD) außerhalb des zentralen Nervensystems (ZNS) bei Kindern, Jugendlichen und Erwachsenen mit Typ A/B oder Typ B indiziert.

Hinweis zur Synopse: Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *saurer Sphingomyelinase-Mangel/Acid Sphingomyelinase Deficiency (ASMD)* durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (*https://www.google.com/*) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Der Suchzeitraum der systematischen Literaturrecherche wurde auf die letzten fünf Jahre eingeschränkt und die Recherchen am 04.04.2025 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Auflistung durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherchen ergaben insgesamt 185 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurde insgesamt eine Referenz eingeschlossen. Es erfolgt eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenz.

3 Ergebnisse

3.1 Cochrane Reviews

Es konnten keine CR im vorliegenden AWG identifiziert werden.

3.2 Systematische Reviews

Es konnten keine SR im vorliegenden AWG identifiziert werden.

3.3 Leitlinien

Geberhiwot, T et al., 2023 [1].

Consensus clinical management guidelines for acid sphingomyelinase deficiency (Niemann–Pick disease types A, B and A/B)

Zielsetzung/Fragestellung

Acid Sphingomyelinase Deficiency (ASMD) is a rare autosomal recessive disorder caused by mutations in the SMPD1 gene. This rarity contributes to misdiagnosis, delayed diagnosis and barriers to good care. There are no published national or international consensus guidelines for the diagnosis and management of patients with ASMD. For these reasons, we have developed clinical guidelines that defines standard of care for ASMD patients.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium; trifft teilweise zu [Patientenvertretung unklar]

  Interessenkonflikte und finanzielle Unabhängigkeit dargelegt; trifft teilweise zu [Angaben zu potentiellen IK fehlen, Angaben zur Finanzierung liegen vor (*Competing interests Sanofi has provided financial support to AD, AL, ES, OL, RG, SCB and TH, research grant to ES and TH, and honorarium to AD, ES, OL, MTV and RG. Honorarium has been provided by Orphazyme to AD and MTV.)]*
- Systematische Suche, Auswahl und Bewertung der Evidenz; trifft zu
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt; trifft zu
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert; trifft zu.

  [These guidelines will be reviewed every 3–5 years.]

Recherche/Suchzeitraum:

- A systematic literature review on ASMD in the last 20 years until December 2021 was carried out using Medline, Embase and the Cochrane Library.
- The following search-string was used for PubMed, with appropriate modifications for the other two databases: (Acid Sphingomyelinase Deficiency[Text Word]) OR (Niemann–Pick B[Text Word]) OR (Niemann–Pick A[Text Word]). Relevant papers which were previously published and considered by the GDG members as important were included.

LoE/GoR:

Table 1 Evidence levels and strength of recommendations

Item	Definition
Level of evidence	
A. High quality evidence	Further research is unlikely to change our confidence in the estimate of effect. Consistent evidence from Randomised Controlled Trials (RCTs) without important limitations or exceptionally strong evidence from observational studies
B. Moderate-quality evidence	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies
C. Low-quality evidence	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Evidence for at least one critical outcome from observational studies, case series, or from RCTs with serious flaws, or indirect evidence, or expert's consensus
Strength of recommendation	
1. Strong recommendation	Recommendation can apply to most patients in most circumstances
2. Weak recommendation	The best course of action may differ depending on circumstances or patient or society values. Other alternatives may be equally reasonable

Empfehlungen

Management

ASMD is not yet curable, but it is a treatable condition. Optimal disease management requires a multidisciplinary, multi-professional team [117] based in a specialist centre, closely liaising with community care providers. The mainstay of therapy is addressing the existing/impending complications and symptom management [118]. Once widely available on the market, Enzyme replacement therapy (ERT) as a disease modifying agent is anticipated to slow the progression of nonCNS manifestations of disease [118, 119].

How is optimal care delivered for a patient with ASMD?

Statement 16: Patients with ASMD exhibit variably progressive multisystem disease and benefit from multidisciplinary and multi-professional follow up from physicians and allied health care professionals with experience in this condition. Wherever possible, patients identified with ASMD should be referred to a centre with expertise in the care of this condition.

- Strength of recommendation: 1
- Level of evidence: A
- Experts' opinion: completely agree (75%), mostly agree (19%), partially agree (6%), mostly disagree (0%) and completely disagree (0%).

Hintergrundinformationen
Experience from other ultra-rare, multisystemic diseases showed that patients who have access to a highly specialised clinical service reported high levels of satisfaction in their care. Patient treatment compliance and clinic attendance was better in a multi-disciplinary clinic compared to the usual standard of care [120]. Depending on the country's health care service setup, level of expertise and patient needs, a multi-disciplinary team (MDT) can be formed to enable ASMD patients to receive a collaborative management plan from a wide range of experts in an integrated manner. Specialists in the different disciplines (Table 4) have to work together to integrate information and care as much as possible. International expert guidelines have been established here to monitor ASMD given the multi-systemic involvement and progressive nature of the disorder. Monitoring goals should be established at diagnosis and reviewed regularly, aimed at identifying and managing disease complications, and enhancing quality of life [119].
How should burden of illness be assessed? The clinical phenotype and life expectancy of patients with ASMD vary widely depending on the spectrum/ type of the disease, age of onset, extents of target organ involvements and pre-existing/impending complications [47]. ASMD type A is the most severe form with a relatively homogenous natural history of rapid progression and short life expectancy [47] [38]. On the other hand, individuals with ASMD type B have a wide range of disease manifestations, variable rate of disease progression, severity level and life expectancy [30–32]. Individuals with ASMD type A/B have a phenotype intermediate between types A and B that typically includes a more slowly progressive neurodegenerative course. Recommendations for clinical monitoring of patients with ASMD have been published [119]. The following assessments should take place at the time of diagnosis or symptom onset and at regular intervals for optimal symptom control and maintain functional capacity (Table 5).

Table 4 Recommended multidisciplinary assessment of patients with ASMD

Discipline	Features of ASMD for which this discipline may be of assistance	Recommended for all ASMD or as needed
Primary care physician	Assist with general medical care; coordinate specialists; provide support for family	All
Metabolic diseases specialist	Diagnosis of ASMD and exclusion of other disorders in the differential diagnosis; Ongoing patient assessment for disease progression and response to therapy. Coordinate the overall care working with primary care physician	All
Neurologist	Assess the possible neurological manifestation of the disease and manage accordingly	All
Hepatologist	Periodic assessments of liver derangements; Manage the impending/existing liver failure	As needed
Haematologist	Assess the risk of bleeding disorder and long term complications	As needed
Pulmonologist	Assess the baseline respiratory functions and periodic assessment for deterioration; manage the pulmonary disease and its complications	As needed
Genetic counsellor	To inform affected persons and their families regarding nature and implications of ASMD to facilitate medical and personal decision making; provide counselling for families as to recurrence risk and options for prenatal diagnosis if desired	All
Lipidologist/cardiologist	Manage the mixed dyslipidemia, and perform cardiovascular risk assessment for indicated primary or secondary prevention interventions	As needed
Psychiatrist/clinical psychologist	Assess for behavioural disturbances, depression and manage accordingly	As needed
Speech and language therapist	Assess for dysphagia and aspiration risk; Speech and feeding therapy for children with neuronopathic phenotypes	As needed
Occupational and physical therapists/rehabilitation physician	Assess and develop aids and home adjustments as needed for patients with communication and physical challenges	As needed
Nutritionist	Periodic assessments of nutritional status in patients who may be losing weight due to dysphagia or side effects of therapy; gastrostomy tube insertion as indicated	As needed
Social worker	Support of patients and families living with disabilities who require enhanced resources in the community	As needed
Developmental and behavioural paediatrician	Assess for the presence or absence of developmental delays in children; recommend appropriate therapies and educational interventions	As needed

Growth and nutrition

Statement 17: The growth of children with ASMD (height, weight and head circumference) should be assessed at regular intervals as part of routine health assessments. In addition, adult patients should undergo a careful assessment of their anthropometric measurements.

- Strength of recommendation: 1
- Level of evidence: A
- Experts' opinion: completely agree (69%), mostly agree (25%), partially agree (6%), mostly disagree (0%) and completely disagree (0%).

Developmental assessments

Statement 18: Children with ASMD should have assessments of their age-appropriate acquisition of developmental milestones. Developmental screens can be performed by primary health care providers, and more formal age-appropriate developmental assessments should be performed as part of MDT assessments.

Those with developmental milestones concern should have accesses to early intervention and development support.

- Strength of recommendation: 1
- Level of evidence: A
- Experts' opinion: completely agree (87%), mostly agree (13%), partially agree (0%), mostly disagree (0%) and completely disagree (0%)

Hintergrundinformationen
Delayed acquisition of developmental milestones is
seen in patients with ASMD type A and common in children with type A/B. Regular evaluation of their motor and cognitive function, speech and language is indicated. Consideration should be given to changes in these abilities that may impact on daily living activities. Testing should be age and functionally appropriate, using

standardised assessment tools. Strategies to ensure the safety of the patient's environment and the availability of support mechanisms are essential to improve the quality of life of the patient/families. Appropriate ongoing education and developmental support into adulthood and beyond is required.

Table 5 Recommended assessments

Recommended assessment	Rationale	Frequency	Recommended for all ASMD or as needed
Baseline history	Establish natural history, systemic involvement, current level of disease severity and estimate rate of progression	At diagnosis	All
Interval history	Establish rate of disease progression; monitor for compliance with and side effects from therapy	3–12 monthly/each visit	As needed
Physical examination	Document growth parameters, assess for neurological features and organomegaly, assess for fatigue, abdominal pain, and/or bleeding tendency at least annually	At diagnosis then 6–12 monthly/each visit	As needed
Nutrition	Evaluation of nutritional status and safety of oral intake	At diagnosis then at each visit	As needed
Pulmonary assessment	Assess recurrent chest infections	At diagnosis then at each visit	All
	Assess for shortness of breath		
	Pulmonary function testing including assessment of diffusing capacity in persons old enough to cooperate	At diagnosis then annually	As needed
	Chest radiograph and/ or high resolution chest CT to assess extent of interstitial lung disease	At diagnosis regardless of age then every 2–4 years	All
Musculoskeletal assessment	Assess for fractures and/or extremity pain	At diagnosis then each visit	All
Neurologic assessment	Comprehensive neurologic evaluation, assess neurologic function and frequency of headaches	At diagnosis then annually	As needed
Ophthalmology evaluation	Presence of cherry-red spots at baseline and document	At diagnosis	All
Cardiac assessment (adult only)	EKG, echocardiogram, coronary angiogram as indicated	At diagnosis	As needed
		Every 3–5 years	
Blood investigations	Serum chemistries including liver transaminases (ALT, AST), albumin, and clotting factors to evaluate for progression of hepatic dysfunction	At diagnosis then at least annually	As needed
	Complete blood count to evaluate for thrombocytopenia, leukopenia, anemia, and increased bleeding		
	Measurement of lipid profile		
Imaging studies	Radiologic measurements of liver and spleen size as needed	At diagnosis then as needed	As needed
	Liver elastography or FibroScan to evaluate for hepatic fibrosis and cirrhosis		
Swallowing assessment	Swallowing assessment in all patients at risk; document presence of dysphagia and aspiration and response to therapy	At diagnosis and then 6 monthly in children; in adults, frequency could be reduced to every	As needed
		12 months if asymptomatic and disease is stable	
Developmental or cognitive assessment	Developmental assessment, monitor developmental progress and educational needs (evaluation for early intervention/ special education)	At diagnosis then at each visit	As needed
	Document baseline degree of cognitive impairment including motor, adaptive, cognitive and speech/language and monitor response to therapy	At diagnosis; 6 monthly in children; 12 monthly in adults	As needed
Neuropsychiatric evaluation	Document psychiatric manifestations and response to therapy	At diagnosis then 6–12 monthly as indicated	As needed

Table 5 (continued)

Recommended assessment	Rationale	Frequency	Recommended for all ASMD or as needed
Family support and resources	Assess need for family support and resources at each visit	At diagnosis then each visit	As needed
	Assess need for community or online resources such as Parent to parent; social work involvement for parental support		
	Home nursing referral		
	Assess for any change in social, domestic, or school or work related activities		

Physical examination

Statement 19: Individuals with ASMD should undergo a comprehensive physical examination including detailed neurological assessment at the time of diagnosis and thereafter on regular interval.

- Strength of recommendation: 1
- Level of evidence: A
- Experts' opinion: completely agree (81%), mostly agree (6%), partially agree (13%), mostly disagree (0%) and completely disagree (0%).

Hintergrundinformationen
Detailed neurologic examination is particularly important for newly diagnosed children, especially when the ASMD type has not yet been established. The presence or absence of neurologic findings may help determine the phenotype and enable more accurate prognostics.

Routine monitoring laboratory tests

Statement 20: Biochemical and haematological abnormalities are common in patients with ASMD and hence they need blood tests at baseline and regular interval. These include but are not limited to, full blood cell count, liver enzymes, vitamin D, lipid profile, clotting markers, enhanced liver fibrosis test, lysosphingomyelin and PPCS.

- Strength of recommendation: 1
- Level of evidence: B
- Experts' opinion: completely agree (44%), mostly agree (44%), partially agree (12%), mostly disagree (0%) and completely disagree (0%).

Hintergrundinformationen
Haematological abnormalities such as thrombocytopenia, leukopenia and anemia are common ranging from 21 to 53% study population [41]. Mixed dyslipidaemia with atherogenic lipoprotein profile is highly suggestive of ASMD. Liver function test abnormalities such as raised transaminases can occur in up to 75% of patients with ASMD [31, 38]. Lysosphingomyelin appears to be a valuable biomarker for overall ASMD disease severity [84].

Evaluation of liver and spleen

Statement 21: Hepatosplenomegaly is present in most ASMD patients at the time of diagnosis. We recommend liver and spleen MRI including volumetric assessment, although ultrasounds can be performed in younger patients and where resource is limited.

- Strength of recommendation: 2
- Level of evidence: B
- Experts' opinion: completely agree (69%), mostly agree (31%), partially agree (0%), mostly disagree (0%) and completely disagree (0%).

Hintergrundinformationen
The most common observation at presentation is splenomegaly (78%) and hepatomegaly (73%) [41]. The sphingomyelin deposition in the liver poses an increased risk of progression to fibrosis, cirrhosis and eventually liver failure and its related complications. Liver failure is the second common cause of death in patients with ASMD of type B [43]. Non-invasive evaluation of liver fibrosis by ultrasound/MRI and elastographic techniques at regular interval is warranted [119].

Evaluation of pulmonary disease

Statement 22: Interstitial lung disease occurs in the majority of ASMD patients at some time in their lives, especially in the younger ones. Chest X ray and high resolution chest CT scan should be performed at baseline and regular interval as required. Impaired -O2/CO2

exchange is reflected by compromised diffusion capacity. This may be associated with shortness of breath and greater disease severity. Chest tomography is the most useful imaging modality to evaluate the interstitial lung disease, with typical ground glass appearance. Pulmonary function tests (especially DLCO –diffusion capacity for carbon monoxide) and exercise testing are important to detect impaired diffusion capacity.

- Strength of recommendation: 1
- Level of evidence: B
- Experts' opinion: completely agree (81%), mostly agree (19%), partially agree (0%), mostly disagree (0%) and completely disagree (0%).

Hintergrundinformationen
Pulmonary pathology in ASMD typically manifests as interstitial lung disease (ILD) caused by sphingomyelin accumulation in alveolar and intra-alveolar macrophages within the alveolar septum. This results in distortion and thickening of the alveolar septum, and impaired -O2/CO2 exchange [121]. Pulmonary dysfunction is a key clinical characteristic of all ASMD phenotypes. Pulmonary involvement affects many patients with ASMD to some degree, with some patients experiencing progressive lung deterioration and respiratory failure [38, 119, 122]. However, several attenuated adult patients may have no evidence of lung disease [30]. For patients with ASMD type A, pulmonary manifestations can include frequent infections (e.g., pneumonia) and respiratory arrest [29]. For patients with ASMD type B and A/B, pulmonary manifestations can include: frequent infections, shortness of breath, and exercise dyspnea and reduced exercise tolerance [38, 41, 47, 122]. Diffusing capacity of carbon monoxide (DLCO) is a clinically meaningful measure of disease burden for patients with ASMD [122]. However, due to the rarity of ASMD and often inadequate diagnostic screening initiatives, available evidence remains limited, especially on mortality/survival, frequency, and timing of significant clinical events [43, 122].

Evaluation of cardiovascular disease

Statement 23: Adult patients with ASMD usually have an atherogenic lipid profile and hence may be at an increased risk of premature cardiovascular events with age. Appropriate assessments should be performed as clinically indicated.

- Strength of recommendation: 2
- Level of evidence: C
- Experts' opinion: completely agree (56%), mostly agree (31%), partially agree (13%), mostly disagree (0%) and completely disagree (0%).

Hintergrundinformationen
Dyslipidemia with low high-density lipoprotein cholesterol, increased low density lipoprotein cholesterol, and hypertriglyceridemia appears to be associated with early atherosclerotic heart disease [46] in line with the general population. To date, increased risk of premature CV events is not proven despite atherogenic lipid profile as well as coronary artery status. Therefore, the use of lipid lowering therapy (e.g. statins) in ASMD patients as a primary prevention needs careful consideration in the context of the overall cardiovascular risk of the individual.

Evaluation of skeletal disease

Statement 24: Individuals with ASMD may be at risk of osteopenia and osteoporosis. Bone density studies could be performed in individuals as clinically indicated.

- Strength of recommendation: 2
- Level of evidence: C
- Experts' opinion: completely agree (63%), mostly agree (31%), partially agree (6%), mostly disagree (0%) and completely disagree (0%).

Hintergrundinformationen
Adults with ASMD type B may have some degree of
osteopenia or osteoporosis. Children with ASMD may also have low Z scores for bone mineral content and density [45]. Pathologic fractures have been reported in some ASMD individuals with severe disease [123].

Disease modifying therapy

Olipudase alfa: is an enzyme replacement therapy addressing the underlying metabolic defect by replacing deficient or defective acid sphingomyelinase. To date, it is the first and only disease modifying therapy for patents with ASMD.

Statement 25: Olipudase alfa, an enzyme replacement

therapy (ERT) using human recombinant acid sphingomyelinase, is indicated as a disease-modifying enzyme replacement therapy for the long-term treatment of noncentral nervous system (CNS) manifestations of ASMD. At the time of writing, olipudase alfa has received

regulatory approval in Brazil, Japan, Europe and the United States of America and is awaiting approval in other countries.

- Strength of recommendation: 1
- Level of evidence: A
- Experts' opinion: completely agree (69%), mostly agree (31%), partially agree (0%), mostly disagree (0%) and completely disagree (0%).

Statement 26: All patients with a confirmed diagnosis of ASMD and significant non-Central Nervous System (CNS) manifestations could be considered for olipudase alfa therapy on an individual basis.

- Strength of recommendation: 1
- Level of evidence: A
- Experts' opinion: completely agree (65%), mostly agree (29%), partially agree (6%), mostly disagree (0%) and completely disagree (0%).

Statement 27: The effectiveness of treatment with olipudase alfa should be monitored with the measurement of growth (in children), the volume of liver and spleen, lung function, haematological markers, plasma lipid profile and disease biomarkers and data should be collected for future treatment guideline development.

- Strength of recommendation: 1
- Level of evidence: A
- Experts' opinion: completely agree (94%), mostly agree (6%), partially agree (0%), mostly disagree (0%) and completely disagree (0%).

Hintergrundinformationen
Four studies of olipudase alfa have been completed. A single-center, open-label, single-ascending-dose trial evaluated the safety of olipudase alfa (0.03–1.0 mg/kg) in 11 adults with ASMD type B (NCT00410566). This study identified 0.6 mg/kg as a maximum tolerated starting dose that supported a dose-escalation strategy [124]. A Phase 1B study assessed safety and tolerability in five adult patients with non neuronopathic ASMD that received escalating doses of olipudase alfa every 2 weeks for 26 weeks (NCT01722526) [125, 126]. A Phase II/III, international multicentre, randomized, double-blind, placebo-controlled trial (ASCEND; NCT02004691/EudraCT 2015-000371-26) enrolled 36 adults with ASMD randomized 1:1 to receive olipudase alfa or placebo intravenously every 2 weeks with intrapatient dose escalation to 3 mg/kg. Primary efficacy endpoints were percent change from baseline to week 52 in percent predicted diffusing capacity of the lung for carbon monoxide and spleen volume. Least square mean percent change from baseline to week 52 favoured olipudase alfa over placebo for percent predicted diffusing capacity of the lung for carbon monoxide (22% vs. 3.0% increases, $P = 0.0004$), spleen volume (39% decrease vs 0.5% increase, $P < 0.0001$), and liver volume (28% vs. 1.5% decreases, $P < 0.0001$) [86].
In addition, (ASCEND-Peds/NCT02292654) study was
designed as phase I/II, international, multicenter, openlabel trial that enrolled 20 paediatrics patients to receive intravenous olipudase alfa every 2 weeks with intrapatient dose escalation to 3 mg/kg. Primary outcome was safety through week 64. In this study in children with ASMD, olipudase alfa was generally well-tolerated with significant improvements in disease pathology across a range of clinically relevant endpoints [85]. The most commonly observed adverse reactions included headache, cough, diarrhoea, and hypotension in adults, and pyrexia, cough, diarrhoea, rhinitis, and abdominal pain in children. Importantly, hypersensitivity reactions including anaphylaxis occurred in some paediatric patients. In summary, olipudase alfa was well-tolerated in children and adults and, after treatment (1 year in adult and 2 years in children), resulted in improved lung function, reductions in spleen and liver volumes, improved platelet counts and lipid profiles, reductions in disease biomarkers, and improved growth (in children) [85, 86, 127–129]. The guideline development group had extensive discussion about olipudase alfa use in patients with acute or rapidly progressive neurologic disease, as they were excluded from the ASCEND-Peds study (NCT02292654/ Sanofi Genzyme) given the inability of the intravenously administered enzyme to cross the blood brain barrier or impact neurologic disease. However, early managed access programs allowed some patients with

visceral and neurologic manifestations of ASMD access to olipudase alfa with a focus on ameliorating visceral signs and symptoms [130, 131]. National patient organizations surveyed parents of children who received olipudase alfa for at least 12 months, including some patients with visceral and neurologic manifestations of ASMD. Data from that survey suggests all parents were satisfied with the therapy and perceived a meaningful benefit in controlling visceral symptoms (submitted manuscript). Some countries have more liberal indications that allow
for olipudase alfa use in all ASMD patients, including infants with acute neurovisceral and rapidly progressive chronic neurovisceral ASMD. As olipudase alfa will not prevent or impact CNS manifestation, it is important that families of infants with rapidly progressive neuronopathic forms of ASMD who are considering olipudase alfa are counselled about the risks, benefits, limitations, and long-term futility of therapy, as well as the option to terminate treatment when progressive neurodegeneration occurs. Alternatives to disease modifying therapy, supportive management, family counselling, and palliative care, should also be discussed. Patients eligible for ERT should undergo disease burden assessment prior to treatment initiation in order to assess the potential benefit of olipudase alfa on the respiratory function, spleen and liver volume, platelet count, growth in children and quality of life measures. Individually tailored treatment goal is agreed between the care givers and patients/families at the outset, and these assessments should be repeated on regular interval. In addition, other issues related to tolerance, treatment adherence and comorbidities should be monitored.

Haematopoietic stem cell transplantation

Statement 28: Variable results have been reported with haematopoietic stem cell transplantation (HSCT) and morbidity such as graft versus host disease (GvHD), infection and renal tubular dysfunction, and mortality associated with HSCT limits its use. HSCT may be useful to correct the metabolic defect, improve blood counts, and reduce increased liver and spleen volumes, but does not address neurologic disease and the revers of growth retardation is uncertain. Therefore, any attempts to perform HSCT in individuals with clinically evident neurologic disease should be considered experimental as it does not correct or stabilize neurologic disease.

- Strength of recommendation: 2
- Level of evidence: C
- Experts' opinion: completely agree (56%), mostly agree (31%), partially agree (13%), mostly disagree (0%) and completely disagree (0%).

Hintergrundinformationen
Symptoms management What optimal symptomatic therapy should be considered for a patient with ASMD deficiency? Liver disease and splenomegaly Statement 29: Liver enlargement with elevated transaminases is common in ASMD, which may progress to fibrosis and cirrhosis in the third to fourth decade. In some severely affected individuals, liver failure may occur resulting in portal hypertension with associated oesophageal varices, ascites, and hepatic encephalopathy. Close monitoring of liver function and early consultation with a hepatologist is recommended as needed. Splenectomy should be avoided.

- Strength of recommendation: 2
- Level of evidence: C
- Experts' opinion: completely agree (81%), mostly agree (19%), partially agree (0%), mostly disagree (0%) and completely disagree (0%).

Hintergrundinformationen
Advanced cases of chronic liver disease (CLD) with
fulminant liver failure were reported in a few adults with ASMD [38, 42]. The rate of progression of liver disease is extremely variable [31, 41, 43]. More research is
needed to determine the cause and rate of progression of advanced CLD in ASMD patients. Liver failure is one of a leading cause of mortality in ASMD patients [38] and adult patients with evidence of transaminitis/fibrosis should be followed by hepatologists. Liver biopsy in persons with evidence of deteriorating liver function may be indicated if non-invasive means to ascertain fibrosis are not available [119]. If patients are known to have advanced CLD then they should be monitored and treated for risk of

gastrointestinal bleeding and surveillance for hepatocellular cancer. The outcomes of liver transplantation have been reported in several individuals with ASMD type B who had progressive liver dysfunction. In addition to improvements in hepatic function and dyslipidemia, significant improvements in lung disease and paediatric growth parameters were observed [41, 119, 132, 133]. Splenectomy on the other hand is not recommended as
it may lead to exacerbation of liver disease and increased sphingomyelin accumulation in the lungs causing progressive respiratory insufficiency. If splenectomy is required due to massive splenomegaly, pressure symptoms, and severe unsustainable hypersplenism, then partial splenectomy or partial splenic arterial embolization are options. If partial or total splenectomy should be performed according to surgical indications, standard postsurgical antibiotic prophylaxis and vaccinations should be used.

Respiratory system

Statement 30: ASMD patients with pulmonary and/or neurological disease are at an increased risk of frequent respiratory infection including aspiration pneumonia and care givers should be vigilant in preventing and/ or promptly managing respiratory infection. Older individuals with ASMD should have their history reviewed for respiratory symptoms and lung function test along with the need for non-invasive ventilation. Vaccination against influenza, COVID-19 and Streptococcus pneumoniae should be encouraged.

- Strength of recommendation: 2
- Level of evidence: C
- Experts' opinion: completely agree (63%), mostly agree (25%), partially agree (12%), mostly disagree (0%) and completely disagree (0%).

Hintergrundinformationen
Respiratory disease is a primary and independent contributor to mortality in ASMD type A (27.7% of cases) [43], and disease burden and morbidity for patients with chronic forms of ASMD [31, 33, 41, 42, 47]. Progressive interstitial lung disease is a prevalent clinical feature of ASMD contributing to decreased QoL and increased disease burden.
Patients with progressive pulmonary disease may
require long-term oxygen therapy. Other treatment for interstitial lung disease (e.g., steroids) and therapeutic lung lavage may be indicated. Endoscopic treatment of bronchial casts may be urgently required. Lung transplantation does not have proven extra benefit. Supporting measures such as smoking cessation should be encouraged. Other treatments for interstitial lung disease (e.g., steroids) have not been well studied [134, 135]. Therapeutic bronchopulmonary lavage for some patients with ASMD type-B has been associated with temporary clinical improvement, but with variable results [117, 134, 135]. Four cases of lung transplantation in ASMD type-B with variable results have been reported [136–139].

Haematology

Statement 31: Bleeding tendency is common but the type and severity of bleeding is highly variable. Consultation with a haematologist in case of severe thrombocytopenia is recommended for evaluation and management.

- Strength of recommendation: 2
- Level of evidence: C
- Experts' opinion: completely agree (69%), mostly agree (31%), partially agree (0%), mostly disagree (0%) and completely disagree (0%).

Hintergrundinformationen
The most common bleeding event is epistaxis and mostly self-limiting. However, significant bleeding event such as post-surgical and trauma-related haemorrhages and life-threatening, liver-disease associated oesophageal variceal disease can occur [38, 43]. Although thrombocytopenia is a common manifestation of ASMD, the platelets are rarely low enough to cause significant bleeding suggesting the presence of additional factors that impact clotting.

Swallowing and diet

Statement 32: Children with neuronopathic ASMD (types A and A/B) should undergo a comprehensive swallowing assessment by a speech and language therapist. Instruction in dietary modification and compensatory postures may be beneficial for individuals with dysphagia. The family should be educated regarding the progressive worsening of swallowing skills and increased risk of aspiration as part of an ongoing care. Nasogastric tube feeding or surgical placement of feeding tube can be considered to enhance caloric intake and possibly reduce the risk of aspiration, although the family should be counselled that this is optional given that ASMD type A is, at present, uniformly fatal.

- Strength of recommendation: 2
- Level of evidence: B
- Experts' opinion: completely agree (69%), mostly agree (31%), partially agree (0%), mostly disagree (0%) and completely disagree (0%).

Irritability and sleep disturbance

Statement 33: Clinicians and caregivers of individuals with ASMD Type A should be aware that there is an increased prevalence of irritability and sleep disturbance affecting quality of life for entire family. Management plans for irritability and sleep disturbance should be considered as indicated.

- Strength of recommendation: 2
- Level of evidence: C
- Experts' opinion: completely agree (69%), mostly agree (31%), partially agree (0%), mostly disagree (0%) and completely disagree (0%).

Chronic pain and fatigue

Statement 34: Chronic pain and fatigue may occur in the majority of ASMD patients at some time in their lives. Optimising pain management and assessment for fatigue should be performed as indicated according to the local standards.

- Strength of recommendation: 2
- Level of evidence: C
- Experts' opinion: completely agree (50%), mostly agree (44%), partially agree (6%), mostly disagree (0%) and completely disagree (0%).

Psychosocial wellbeing

Statement 35: Clinicians, caregivers and individuals with ASMD should be aware that there is an increased prevalence of behavioural problems and other psychiatric disorders such as anxiety and depression in ASMD. There should be a low threshold for referral to a clinical psychology/psychiatric team as appropriate, and for the use of both non-pharmacological and/or pharmacological treatments.

- Strength of recommendation: 1
- Level of evidence: B
- Experts' opinion: completely agree (62%), mostly agree (19%), partially agree (0%), mostly disagree (19%) and completely disagree (0%).

Hintergrundinformationen

As with most ultra-rare diseases, there is a limitedrobust data regarding the disease burden and the impact on the psychosocial wellbeing of an individual with ASMD and their immediate family members [49]. In a small study based on interviews with patients and caregivers, numerous psychosocial stressors such as social

isolation, peer rejection, chronic pain, fatigue and living with a life-threatening disease were associated with high level of stress, anxiety and depression [48]. In addition, children with ASMD type A show increased signs of irritability, prolonged crying and sleep disturbance [29]. Similarly, depression and psychosis requiring antidepressant/psychotic therapies may occur in adult patients with ASMD [47].

Transition, family and reproductive care and advanced care planning Transition Statement 36: Most children with chronic visceral ASMD are expected to reach adulthood with complex medical and psychosocial needs. The process of transition from paediatric to adult services should begin early and gradually progress allowing patients and their caregivers to build a relationship and develop confidence with their adult metabolic team. Therefore, the clear communication and trust between these two teams would be highly beneficial for patients to feel continuously cared for at the highest standards by their new team. It must also include appropriate services in the community to provide a seamless transition from childhood to adult life. Individuals with ASMD may benefit from a detailed assessment identifying barriers to independence.

- Strength of recommendation: 1
- Level of evidence: A
- Experts' opinion: completely agree (69%), mostly agree (31%), partially agree (0%), mostly disagree (0%) and completely disagree (0%).

Family and reproductive care

Statement 37: Once the SMPD1 pathogenic variants have been identified in an affected family member, diagnostic testing of all at-risk family members is warranted to allow for early diagnosis and treatment of ASMD. All patients identified pre-symptomatically should be referred to specialist centres for surveillance and early detection of disease progression.

- Strength of recommendation: 1
- Level of evidence: A
- Experts' opinion: completely agree (75%), mostly agree (25%), partially agree (0%), mostly disagree (0%) and completely disagree (0%).

Hintergrundinformationen
Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an SMPD1 pathogenic variant and to allow testing for at risk relatives. Either test for the familial SMPD1 pathogenic variants or measure residual acid sphingomyelinase enzyme activity is appropriate to detect affected individuals. Individuals at risk will require careful genetic counselling by genetics professionals to inform affected persons and their families regarding nature and implications of ASMD to facilitate medical and personal decision making.

Statement 38: Prenatal ASMD testing for a pregnancy at increased risk should be offered to all at risk couples, subject to local protocols and laws. Molecular testing for the familial SMPD1 variants using chorionic villus sampling (CVS) or amniotic fluid sampling is the most common means of testing at risk pregnancies. Biochemical prenatal diagnosis by testing of ASM enzyme activity in CVS or cultured amniocytes may also be used for at risk pregnancies.

- Strength of recommendation: 2
- Level of evidence: B
- Experts' opinion: completely agree (63%), mostly agree (31%), partially agree (6%), mostly disagree (0%) and completely disagree (0%).

Hintergrundinformationen
The determination of genetic risk and discussion of the

availability of prenatal/preimplantation genetic testing should be carried out before pregnancy. Genetic counselling (including discussion of potential risks to offspring and reproductive options) should be offered to young adults who are affected, are carriers, or are at risk of being carriers.

Advance care planning

Statement 39: Specialist centre care providers, family physician/ paediatrician, health care decision makers, local palliative care services and patient advocates should develop close working links to select treatments and develop disease management plans that address patients' holistic needs in order to support individuals, caregivers and families with ASMD through the lifespan, including: (a) advance care planning with regular updating, (b) proper flow of communication and information for patients and their families, and (c) a designated point of contact for each stage in their care pathway. An individual identified as being near the end of life may benefit from ongoing access to palliative care services including for symptom control, respite, psychological and spiritual support.

- Strength of recommendation: 1
- Level of evidence: A
- Experts' opinion: completely agree (81%), mostly agree (19%), partially agree (0%), mostly disagree (0%) and completely disagree (0%).

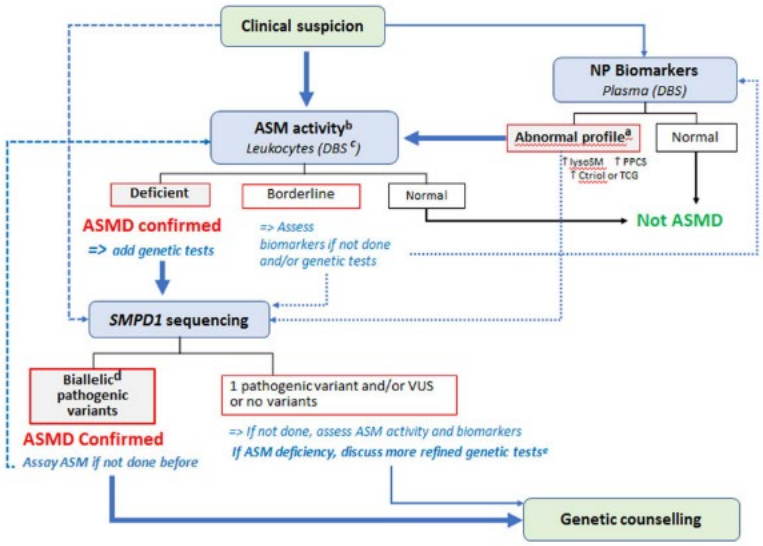

Fig. 1 Algorithm for the laboratory diagnosis of ASMD. (**a**) Significant increase of 3β,5α,6β-cholestane-triol (C-triol), 7-ketocholesterol (7-KC), 3β,5α,6β-trihydroxy-cholanoyl-glycine (TCG), lysosphingomyelin (lyso-SM), *N*-palmitoyl-*O*-phosphocholine-serine (PPCS). A difference with an NPC profile is the normal or slightly elevated lyso-SM level in the latter. Other causes of elevated C-triol levels include cerebro tendinous xanthomatosis (CTX) and acid lipase deficiency. (**b**) LC–MS/MS (or radioisotopic) preferred methods (see Statement 13). (**c**) Recommendation for ASM in DBS to be confirmed on leukocytes or by genetic testing. (**d**) Importance of parental study. (**e**) MLPA/RNA analysis. VUS: Variant of uncertain significance

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 04 of 12, April 2025) am 04.04.2025

#	Suchschritt
1	[mh ^"Lysosomal Storage Diseases"]
2	[mh ^"Lysosomal Storage Diseases, Nervous System"]
3	((Neurovisceral OR visceral OR lysosomal OR lipid* OR sphingolipid*) NEAR Storage NEAR (Disorder* OR Disease*)):ti,ab,kw
4	[mh ^"Sphingolipidoses"]
5	Sphingolipidos*:ti,ab,kw
6	[mh "Niemann-Pick Diseases"]
7	(Niemann* AND Pick*):ti,ab,kw
8	((Acid OR deficien* OR lipidos*) AND Sphingomyelin*):ti,ab,kw
9	(ASMD OR (ASM AND Deficienc*)):ti,ab,kw
10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
11	#10 with Cochrane Library publication date from Apr 2020 to present, in Cochrane Reviews

Leitlinien und systematische Reviews in PubMed am 04.04.2025

verwendete Suchfilter für Leitlinien:
Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.

verwendete Suchfilter für systematische Reviews:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 15.01.2025.

#	Suchschritt
	Leitlinien
1	"Lysosomal Storage Diseases"[mh:noexp]
2	"Lysosomal Storage Diseases, Nervous System"[mh:noexp]
3	(Neurovisceral[tiab] OR visceral[tiab] OR lysosomal[tiab] OR lipid*[tiab] OR sphingolipid*[tiab]) AND Storage[tiab] AND (Disorder*[tiab] OR Disease*[tiab])
4	"Sphingolipidoses"[mh:noexp]
5	Sphingolipidos*[tiab]
6	"Niemann-Pick Diseases"[mh]
7	Niemann*[tiab] AND Pick*[tiab]
8	(acid[tiab] OR deficien*[tiab] OR lipidos*[tiab]) AND sphingomyelin*[tiab]
9	ASMD[tiab] OR (ASM[tiab] AND deficien*[tiab])

#	Suchschritt
10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
11	(#10) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[ti] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
12	(#11) AND ("2020/04/01"[PDAT] : "3000"[PDAT])
13	(#12) NOT ("retracted publication"[pt] OR "retraction notice"[pt] OR "retraction of publication"[pt] OR "preprint"[pt])
	systematische Reviews
14	(#10) AND ("systematic review"[pt] OR "meta-analysis"[pt] OR "network meta-analysis"[mh] OR "network meta-analysis"[pt] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR (("evidence-based medicine"[mh] OR evidence synthes*[tiab]) AND "review"[pt]) OR ((("evidence based"[tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR "technical report"[pt] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
15	(#14) AND ("2020/04/01"[PDAT] : "3000"[PDAT])
16	(#15) NOT "The Cochrane database of systematic reviews"[Journal]
17	(#16) NOT ("retracted publication"[pt] OR "retraction notice"[pt] OR "retraction of publication"[pt] OR "preprint"[pt])
	systematische Reviews ohne Leitlinien
18	(#17) NOT (#13)

Iterative Handsuche nach grauer Literatur, abgeschlossen am 04.04.2025

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)
- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

Referenzen

1. **Geberhiwot T, Wasserstein M, Wanninayake S, Bolton SC, Dardis A, Lehman A, et al.** Consensus clinical management guidelines for acid sphingomyelinase deficiency (Niemann-Pick disease types A, B and A/B). Orphanet J Rare Dis 2023;18(1):85.

[A] **Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, et al.** PRISMA-S: an extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews. Syst Rev 2021;10(1):39. https://doi.org/10.1186/s13643-020-01542-z

[B] **McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C.** PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol 2016;75:40-46. https://doi.org/10.1016/j.jclinepi.2016.01.021

Beteiligung von Fachgesellschaften und der AkdÄ zu Fragen der Vergleichstherapie nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

Verfahrens-Nr.: 2025-B-083

Verfasser	
Name der Institution	**Gf Neuropädiatrie (GNP)**
Datum der Erstellung	**23. April 2025**

Indikation
Als Enzymersatztherapie zur Behandlung von Manifestationen eines Mangels an saurer Sphingomyelinase (ASMD) außerhalb des zentralen Nervensystems (ZNS) bei Kindern, Jugendlichen und Erwachsenen mit Typ A/B oder Typ B.
Fragen zur Vergleichstherapie
Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus? *(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)*
Der saure Sphingomyelinase-Mangel (*Acid Sphingomyelinase Deficiency*, ASMD), früher bekannt als M. Niemann-Pick Typ A, A/B und B, ist eine lysosomale Speicherkrankheit, die durch das biallelische Vorliegen (wahrscheinlich) pathogener Varianten im *SMPD1*-Gen verursacht wird. Diese Varianten führen zu einem Mangel an saurer Sphingomyelinase, einem Enzym, das für den Abbau von Sphingomyelin verantwortlich ist. Infolgedessen kommt es zu einer Akkumulation von Sphingomyelin in verschiedenen Organen wie im Gehirn, Leber, Milz, Lunge und Knochenmark, die zu krankheitstypischen Symptomen führen. **Der Behandlungsstandard in Deutschland bei ASMD außerhalb des zentralen Nervensystems (ZNS) bei Kindern, Jugendlichen und Erwachsenen mit Typ A/B oder Typ B ist zurzeit die Enzymersatztherapie (EET) mit dem Wirkstoff/Präparat Olipudase alfa (Xenpozyme®). Diese Therapie ist sowohl durch die *U.S. Food and Drug Administration* (FDA) als auch die *European Medicines Agency* (EMA) zur Behandlung der ASMD zugelassen. Die Zulassung der FDA unterscheidet sich jedoch von der Zulassung der EMA: Olipudase alfa (Xenpozyme®) ist von der FDA für die nicht-zentralnervösen Manifestationen der ASMD zugelassen – unabhängig vom Typ der Erkrankung [1]. Von der**

EMA ist Olipudase alfa (Xenpozyme®) jedoch nur für die nicht-zentralnervösen Manifestationen der ASMD Typen A/B und B zugelassen [2].

Olipudase alfa wurde in drei klinischen Studien mit ASMD untersucht:

Die erste Studie (ASCEND) [3] untersuchte den Nutzen und die Nebenwirkungen von Olipudase alfa bei erwachsenen Patienten mit ASMD. In dieser Studie erhielten 36 erwachsene Patient:innen 52 Wochen lang alle zwei Wochen intravenös entweder Olipudase alfa oder Placebo. Somit handelte es sich bei dieser Studie um eine randomisierte, Placebo-kontrollierte, doppelblinde Phase 2/3-Studie.

Die zweite Studie (ASCEND-Peds) [4] untersuchte den Nutzen und die Nebenwirkungen von Olipudase alfa bei pädiatrischen Patient:innen. Dabei erhielten 20 pädiatrische Patient:innen Olipudase alfa intravenös einmal alle 2 Wochen über 64 Wochen.

Die dritte Studie [5] war eine Erweiterung der zweiten Studie, in der Nutzen und Nebenwirkungen von Olipudase alfa bei pädiatrischen Patient:innen untersucht wurden. Hierbei handelte es sich um eine offene Langzeitstudie, in der die pädiatrischen Patient:innen, die Studie 2 abgeschlossen hatten, weiter untersucht wurden.

Der Nutzen von Olipudase alfa wurde in allen o.g. Studien durch Bewertung der Kohlenmonoxid-Diffusionskapazität der Lunge (DL_{CO}), des Milzvolumens, des Lebervolumens und der Thrombozytenzahl bewertet.

In Deutschland wurde Olipudase alfa (Xenpozyme®) am 16. März 2023 in die Arzneimittel-Richtlinie aufgenommen, was seine Erstattungsfähigkeit durch die gesetzliche Krankenversicherung sicherstellt [6].

Die Behandlung mit Olipudase alfa (Xenpozyme®) wird in Deutschland in der Regel in spezialisierten Kompetenzzentren für seltene Erkrankungen eingeleitet. Diese Zentren verfügen über umfangreiche Erfahrung in der Diagnose und Behandlung von ASMD. Eine Liste der spezialisierten Kliniken und Zentren, die sich mit der Erkrankung ASMD (Morbus Niemann-Pick Typ A, A/B, B) beschäftigen, ist unter [7] zu finden.

Die Behandlung mit Olipudase alfa (Xenpozyme®) wird bei Erwachsenen (≥ 18 Jahren) mit einer Dosierung von 0,1 mg/kg Körpergewicht und bei Kindern und Jugendlichen (< 18 Jahren) mit einer Dosierung von 0,03 mg/kg Körpergewicht begonnen und nach dem in der Fachinformation angegebenen Schema [8] alle 2 Wochen bis zu einer Erhaltungsdosis von 3 mg/kg Körpergewicht/alle 2 Wochen gesteigert. Bei Patienten mit einem BMI ≤ 30 kg/m2 wird das tatsächliche Körpergewicht zugrunde gelegt. Bei Erwachsenen sowie Kindern und Jugendlichen mit einem Body-Mass-Index (BMI) > 30 kg/m^2 wird das Körpergewicht zur Berechnung der Olipudase alfa (Xenpozyme®)-Dosis mithilfe der folgenden Methode (für Dosissteigerungs- und Erhaltungsphase) geschätzt:

Körpergewicht (kg) für die Dosisberechnung = 30 × (tatsächliche Körpergröße in $m)^2$.

Nach Erreichen der Erhaltungsdosis und bei klinischer Stabilität kann die Therapie wohnortnah oder unter bestimmten Bedingungen auch als Heimtherapie fortgesetzt werden [8].

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen in der o.g. Indikation, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?
(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)

Die Standardtherapie für die nicht-zentralnervösen Manifestationen der ASMD Typ A/B und B stellt, wie oben beschrieben, die Enzymersatztherapie (EET) mit Olipudase alfa (Xenpozyme®) dar. Eine kurative Therapie für ASMD Typ A, A/B und für Typ B existiert weiterhin nicht. An dieser Stelle soll erwähnt werden, dass der Wirkstoff „Olipudase alfa" die Blut-Hirn-Schranke nicht überwinden kann. Somit hat sie keine Wirkung auf die neurologischen Symptome der Erkrankung.

Vor der Zulassung der EET mit Olipudase alfa (Xenpozyme®) war eine gezielte bzw. spezifische Therapie für ASMD nicht verfügbar. So sind in der Literatur Fälle beschrieben, bei denen eine hämatopoetische Stammzelltransplantation (HSCT) durchgeführt worden sind. Eine HSCT kann den Enzymdefekt korrigieren, das Blutbild verbessern und das vergrößerte Leber- und Milzvolumen verringern, stabilisiert aber nicht die neurologische Erkrankung, verzögert nur deren Verlauf [9, 10, 11]. Die mit der HSCT verbundene Morbidität und Mortalität schränken ihre Anwendung ein. Die HSCT für ASMD wird wahrscheinlich überflüssig, da nun eine EET zur Verfügung steht.

Eine Behandlungsindikation besteht bei der ASMD Typ A/B und Typ B insbesondere bei Vorliegen einer Splenomegalie (Milzvergrößerung) mit klinischen Einschränkungen oder erhöhter Rupturgefahr, einer Hepatomegalie mit Leberfunktionsstörung, einer Lungenerkrankung (interstitielle Lungenerkrankung) mit Einschränkung der Lungenfunktion, einer Thrombozytopenie oder Anämie, einer Wachstumsverzögerung bei Kindern und/oder bei einer erhöhter Chitotriosidase-Aktivität im Serum/Plasma sowie erhöhter Konzentration der Speichersubstanz lyso-SM [12]. Da in Deutschland kein Neugeborenenscreening (NGS) für ASMD durchgeführt wird, werden Patient:innen in der Regel durch selektives Screening bei o.g. Beschwerden diagnostiziert. Somit sind diese bei Diagnosestellung symptomatisch, sodass die Therapieindikation in den meisten Fällen bereits bei Diagnosestellung gegeben ist.

Die am häufigsten berichteten unerwünschten Arzneimittelwirkungen (UAWs) unter einer Therapie mit Olipudase alfa (Xenpozyme®) sind Husten, Fieber, Kopfschmerzen, Gelenkschmerzen, Durchfall und niedriger Blutdruck. Schwere Überempfindlichkeitsreaktionen und Anaphylaxie wurden bei einer Minderheit von Personen beobachtet [9]. Diese UAWs müssen bei der Behandlungsentscheidung berücksichtigt werden. Bei Überempfindlichkeitsreaktionen gegenüber Olipudase alfa (Xenpozyme®) muss eine Prämedikation mit Antihistaminika und/oder Kortikosteroiden vor jeder intravenösen Gabe erfolgen.

Ein anderer Punkt, der bei der Therapie mit Olipudase alfa (Xenpozyme®) berücksichtigt werden sollte, ist, dass es sich hierbei um eine lebenslange, zwei-wöchentliche und intravenöse Therapie handelt. So ist, v.a. bei Kindern, ein sicherer intravenöser Zugang

notwendig. Bei kleineren Kindern kann dies eine Hürde darstellen, in solchen Fällen sollte die Notwendigkeit eines zentralen Zugangs (z.B. Portsystem) erwogen werden.

Zusätzlich zu der EET sollen weitere symptomatische Therapien für das Wachstum (z.B. regelmäßige Ernährungsberatung, Nasogastralsonde, PEG-Sonde), für die Leberfunktionsstörungen (z.B. Lebertransplantation [13]) mit/ohne Blutungsneigung (z.B. Gabe von Vitamin K), für die Lungenerkrankung (z.B. Sauerstoff-Supplementation), für die Dyslipidämie (z.B. Behandlung mit Statinen) und für die Osteopenie (z.B. Calcium- und Vitamin D-Supplementation) in Erwägung gezogen werden [9].

Referenzliste:

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