Clinical Commissioning Policy Statement
Vestronidase alfa for Mucopolysaccharidosis Type VII (MPS, Sly syndrome) (infantile) URN (2202) [210401UPS]

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Commissioning position

Summary

Vestronidase alfa is recommended to be available as a routine commissioning as a treatment option for infants with MPS VII within the criteria set out in this document.

Information about Vestronidase alfa

The intervention

Enzyme replacement therapy (ERT) with vestronidase alfa, a recombinant form of human β-glucuronidase, is the first disease-specific treatment for MPS VII. It works by replacing the missing enzyme (beta-glucuronidase) in patients with MPS VII, helping to break down glycosaminoglycans (GAGs) and stopping them building up in the body.

Intravenous vestronidase alfa was designated as an orphan medicine on 21 March 2012 and is approved for the treatment of MPS VII in the EU (non-neurological manifestations only) (European Medicines Agency, 2020). It is used after birth to maximise the possibility that an affected infant will survive the neonatal period and become suitable for haemopoietic stem cell transplant (HSCT). HSCT provides a long-term treatment for the condition and, unlike vestronidase alfa, can positively impact the development of neurological disease. Evidence in other MPS disorders shows that early HSCT can slow down/prevent progression of neurological disease and this is now standard of care for early diagnosed MPS I and for antenatally diagnosed MPS II. The use of ERT prior to HSCT is also well established in these conditions (MPS I and MPS II) to improve the infant's general condition and reduce the risk of the HSCT process. HSCT would not be possible in babies with MPS VII presenting with hydrops fetalis because the hydrops makes them too sick to survive the transplant procedure.

Committee discussion

Clinical Panel considered the clinical evidence summary and agreed with a recommendation for urgent routine commissioning.

The condition

MPS VII is a life-threatening disease with many patients dying in early childhood. It is also debilitating due to the physical and skeletal abnormalities that occur. It is an inherited disease caused by a lack of the enzyme beta-glucuronidase. It is extremely rare; in the UK and MPS VII is the rarest mucopolysaccharidosis with an average of only one baby every 10 years born with the disease (MPS Society, 2022). Beta-glucuronidase is an enzyme which is needed to break down GAGs in the body. If the enzyme is not present, GAGs cannot be broken down and they

build up in the cells and damage them. This causes a wide range of problems such as short stature, skeletal abnormalities, joint stiffness, enlarged spleen and liver, lung infections, heart problems and hernias. Patients usually die within the first year of life, although some survive into their teenage years. Infants with a severe form may experience hydrops fetalis, or abnormal accumulation of body fluids in various tissues (Khan et al., 2017).

Current treatments

There is no approved standard treatment for this patient population. Patients with MPS VII would receive supportive care from a centre approved for the management of patients with Lysosomal Storage Disorders (LSDs) including multidisciplinary team (MDT) input to manage individual symptoms/complications. Individual cases that might benefit from HSCT would be discussed in an MDT and if appropriate would be referred for HSCT on a case-by-case basis. Infants with hydrops fetalis specifically would receive either palliative care only until their demise or supportive neonatal intensive care until their hydrops resolves in which case referral for HSCT might be considered. However, the mortality rate in this subgroup of patients is extremely high and it is expected that most patients presenting in this way would die without ERT.

Comparators

There are no alternative disease modifying interventions available for infantile MPS VII. Infants who do not respond to supportive care only would die without treatment.

Evidence summary

The Three Paper Summary is presented in Appendix 1. The outcomes are summarised below:

Outcome	Summary
Urinary glycosaminoglycan (GAG) excretion	Three papers including a total of 13 patients reported sustained reductions in urinary GAG excretion with vestronidase alfa.
Dysmorphia	One of the included papers (n=1) reported an improvement in dysmorphia after one year of vestronidase alfa.
Organ involvement	One of the included papers (n=1) reported an improvement in hepatomegaly and a partial improvement in spleen size after one year of vestronidase alfa. There was no hepatosplenomegaly or other organ involvement at last follow-up at four years old (following treatment with vestronidase alfa between ages four and 18 months and a haematopoietic stem cell transplant at 13 months).
Infections	One of the included papers (n=1) reported no infections after one year of vestronidase alfa.
Bone involvement and growth	One of the included papers (n=1) reported stabilisation of bone signs after one year of vestronidase alfa and a stabilised growth curve at last follow-up at four years old (following treatment with vestronidase alfa between ages four and 18 months and a haematopoietic stem cell transplant at 13 months).
Auditory invoked potentials	One of the included papers (n=1) reported bilateral partial deafness at two years of age and normal auditory evoked potential testing at last follow-up at four years old (following treatment with vestronidase alfa between ages four and 18 months and a haematopoietic stem cell transplant at 13 months).
Neurological evaluation and development	One of the included papers (n=1) reported that neurological examination was close to normal at one year old, after eight months of vestronidase alfa. Language, psychomotor development and scholarship were normal at last follow-up at four years old (following treatment with vestronidase

	alfa between ages four and 18 months and a haematopoietic stem cell transplant at 13 months).
Multi-domain response	One of the included papers reported that ten of the 12 patients had a clinically meaningful improvement in at least one of the six multi-domain responder index (MDRI) domains (the six-minute walk test, forced vital capacity, shoulder flexion, visual acuity and fine motor and gross motor proficiency). A second included paper, reporting an extension to this study, found that improvements in overall MDRI score were sustained at up to 144 weeks follow-up.
Fatigue	One of the included papers reported an improved fatigue score in nine of 12 patients at some point during the study. A second included paper, reporting an extension to this study, found that improvements in fatigue score were sustained at up to 144 weeks follow-up. The improvement was described as clinically meaningful in four patients for at least one follow-up timepoint.
Modified multi-domain response with fatigue	One of the included papers (n=12) reported an improvement in a modified MDRI score with fatigue added after 24 weeks of vestronidase alfa.
Safety	One of the included papers (n=12) reported that all patients experienced an adverse effect during treatment with vestronidase alfa, with 75% considered to be treatment related. Two of the included papers with a total of 12 patients each reported one treatment-related serious adverse event (not life-threatening). The third included paper reported no adverse effects in one patient.

Adverse events

Adverse events in the literature are mild to moderate and include a risk of anaphylaxis.

Implementation

Criteria

Inclusion criteria

Infants with a diagnosis of MPS VII by biochemical/genetic testing will be evaluated for the capacity to benefit from this treatment.

Exclusion criteria

Illness evaluated as too severe to have any chance of benefit

Starting criteria

Patients that meet the inclusion criteria should be considered for treatment with vestronidase alfa. These patients should be treated under the care of a specialist LSD centre MDT with input from other specialists including (but not limited to) orthopaedic surgeons, physiotherapists, dietitians, specialist nurses, neurosurgeons, cardiologists, respiratory paediatricians, general surgeons and ENT surgeons.

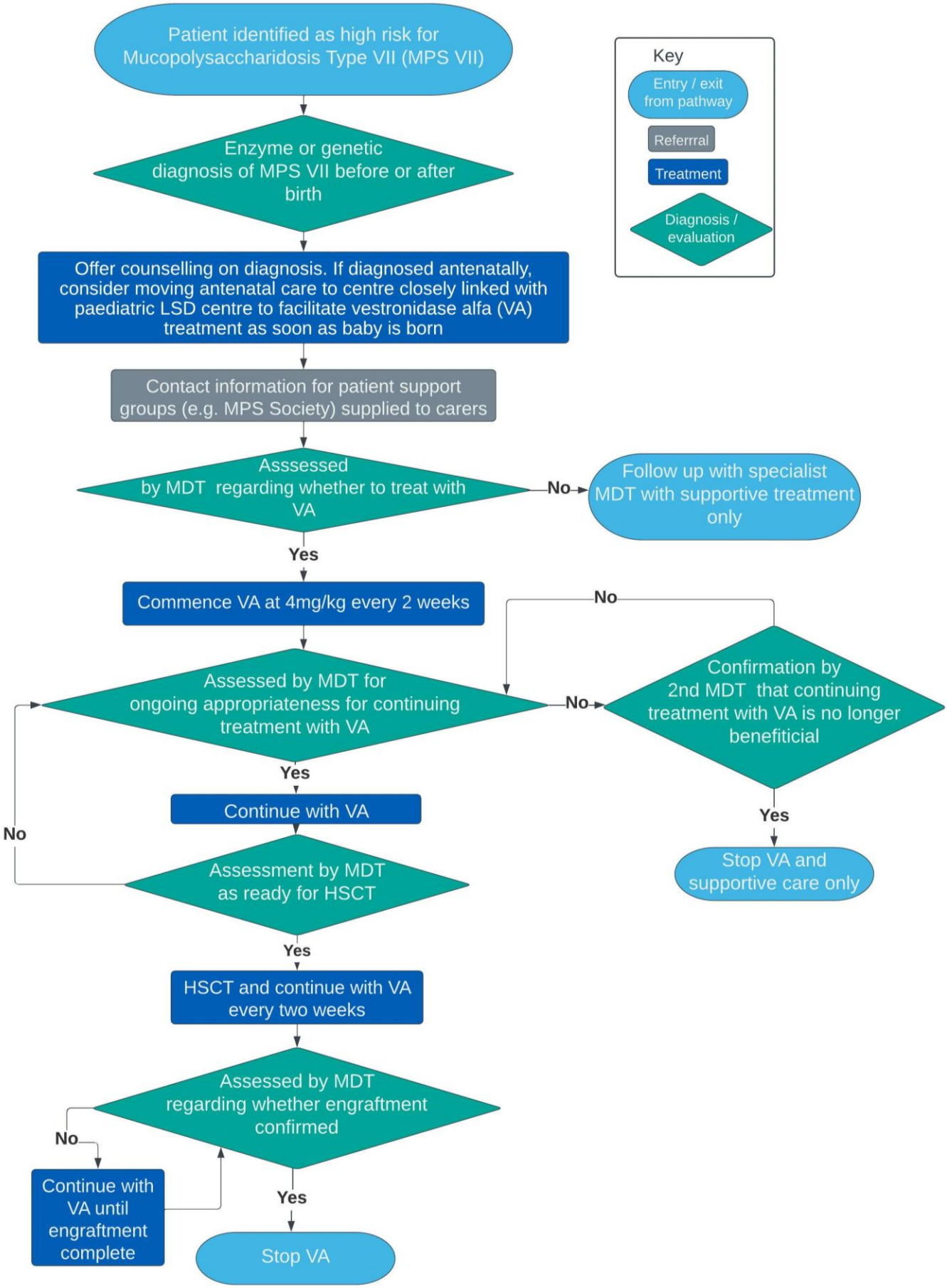
If the MDT agrees ERT is indicated, the patient would commence ERT, receiving the licensed dose of 4mg/kg every 2 weeks. When/if infants stabilise, they will be managed as outpatients at the specialist LSD centre. The infusions should be given in hospital until a time that they are well tolerated at which stage the patient would be expected to transition to home infusions provided initially by a homecare nursing company on the LSD framework.

Stopping criteria

Treatment with vestronidase alfa should be stopped by the specialist MDT in any of either of the following circumstances:

- Engraftment is confirmed after HSCT.
- Progression of the disease indicates that treatment is no longer beneficial. This may include (but is not restricted to) progression of non-neurological disease despite enzyme replacement therapy (rendering the child unsuitable for HSCT), development of rapid neurological deterioration, development of any other condition which would contraindicate future HSCT, and recurrent allergic/anaphylactic reactions to enzyme replacement therapy which cannot be adequately treated by any other means. A decision to stop treatment prior to HSCT must be made in collaboration with a specialist MDT from at least one independent paediatric LSD centre

Patient Pathway



Governance arrangements

This policy should be used in conjunction with the NHS England Specialised Services Lysosomal storage disorders service (Children).

Provider organisations must register all patients using prior approval software and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined.

Recommendations for data collection

Activity data will be collected through the highly specialised reporting template which will include patient numbers and whether the patient proceeded to HSCT.

Mechanism for funding

Vestronidase alfa for the treatment of MPS VII within the criteria in this document will be commissioned and funded by NHS England Specialised Commissioning under existing arrangements for the provision of specialised services.

Policy review date

This is a policy statement, which means that the full process of policy production has been abridged: a full independent evidence review has not been conducted; and public consultation has not been undertaken. If a review is needed due to a new evidence base then a new Preliminary Policy Proposal needs to be submitted by contacting england.CET@nhs.net.

Links and updates to other policies

Not applicable.

Equality statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities

Definitions

Hematopoietic stem cell transplantation (HSCT):	This is a form of stem cell transplantation that is used to treat certain patients with a range of malignant and non-malignant blood-related disorders. It involves the use of stem cells (from the patient or a donor).

References

EUROPEAN MEDICINES AGENCY. 2020. *Mepsevii (vestronidase alfa): An overview of Mepsevii and why it is authorised in the EU* [Online]. Available: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu312973#overview-section [Accessed 28/02/2022].

KHAN, S. A., PERACHA, H., BALLHAUSEN, D., WIESBAUER, A., ROHRBACH, M., GAUTSCHI, M., MASON, R. W., GIUGLIANI, R., SUZUKI, Y., ORII, K. E., ORII, T. & TOMATSU, S. 2017. Epidemiology of mucopolysaccharidoses. *Mol Genet Metab,* 121**,** 227-240.

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Appendix 1: 3 Paper Evidence Summary

Narrative summary of papers presented for review

Three papers were presented for review by NHS England. Paper 1 is a case report of a boy, born in France, who was diagnosed with MPS VII at two weeks of age. He started vestronidase alfa at four months old followed by haematopoietic stem cell transplantation at 13 months old. Paper 2 is a 'blind start' trial which randomised 12 patients with MPS VII (aged 8 to 25 years) to one of four groups. The groups crossed from placebo to active treatment with vestronidase alfa at different blinded timepoints with efficacy assessed by comparing the last assessment before commencement with vestronidase alfa (baseline) to after 24 weeks of treatment. It is not clear which country or countries this trial was conducted in. Paper 3 reports the results of an open-label extension study to the trial presented in Paper 2. In this extension study the 12 patients received vestronidase alfa for up to an additional 144 weeks after completion of the initial trial.

Paper 1: Dubot et al 2019. First report of a patient with MPS type VII, due to novel mutations in GUSB, who underwent enzyme replacement and then hematopoietic stem cell transplantation

This paper reports a case report of a boy with MPS VII who was born in France. The patient was diagnosed with MPS VII at two weeks of age and started enzyme replacement therapy with fortnightly vestronidase alfa (4mg/kg) at four months old. At the point of treatment initiation with vestronidase alfa the patient had a coarse face, hepatosplenomegaly and bone deformities but was without cardiac involvement, respiratory involvement or corneal lesion. Magnetic resonance imaging was normal but a slight axial hypotonia was observed. He received a haematopoietic stem cell transplantation at 13 months old with unrelated donor umbilical cord blood. Treatment with vestronidase alfa was stopped at 18 months of age. The patient was four years old at last follow-up.

Paper 2: Harmatz et al 2018. A novel blind start study design to investigate vestronidase alfa for mucopolysaccharidosis VII, an ultra-rare genetic disease

This paper reports a blind start trial of 12 patients with MPS VII randomised to one of four groups (three patients per group). All patients received a minimum of 24 weeks fortnightly treatment with vestronidase alfa (4mg/kg). The four groups had a variable placebo run-in period so that patients were blinded to when they commenced active treatment. Group A commenced active treatment at week 1, group B at week 8, group C at week 16 and group D at week 24. After commencing active treatment patients continued to receive vestronidase alfa for the remainder of the 48-week study period. However, efficacy for all patients was assessed by comparing the last assessment before commencement with vestronidase alfa (baseline) to after 24 weeks of treatment. The mean age of patients at informed consent was 15.5 years (standard deviation 5.5; median 14.0, range 8.4 to 25.2). The authors stated that the patients in this study had highly variable disease manifestations and levels of impairment. The location or locations of the study was not stated but it was described as multinational in a related publication (Paper 3). The year(s) of treatment were not stated.

Paper 3: Wang et al 2020. The long-term safety and efficacy of vestronidase alfa, rhGUS enzyme replacement therapy, in subjects with mucopolysaccharidosis VII

This paper reports the results of an open-label extension study to the trial presented in Paper 2 in which patients had received between 24 and 48 weeks of vestronidase alfa. All 12 of the patients who participated in the original blind start trial enrolled in the extension study. However, two patients enrolled in the extension study after a 13-month delay (hiatus from vestronidase alfa). Patients received 4mg/kg of vestronidase alfa fortnightly. Three patients (25%) completed the full 144 weeks of the extension study and eight patients (67%) ended study participation to switch to commercially available vestronidase alfa (two at week 40, five between weeks 102

and 114 and one at week 138). One patient (8%) discontinued after one treatment with vestronidase alfa in the extension study due to non-compliance.

Effectiveness

Urinary glycosaminoglycan (GAG) excretion

Dubot et al 2019 reported a decrease in urinary chondroitin sulfate-dermatan sulfate and heparan sulfate at weeks 2, 4, 6, 8 and 12 after initiation of vestronidase alfa (n=1). The figures were only displayed graphically. However, the decrease in chondroitin sulfate- dermatan sulfate appeared to be from approximately 60 mg/mmol creatinine at baseline (week 0) to approximately 20 mg/mmol creatinine (indicated as being within the “range of control values” in the graph) at week 12. The decrease in heparan sulfate appeared to be from approximately 5 mg/mmol creatinine to approximately 2.5 mg/mmol creatinine (indicated as being above the “range of control values” in the graph) at week 12.

Dubot et al also reported that urinary GAG levels were normal at last follow-up at four years old (no further detail reported). Vestronidase alfa was received between the ages of four months and 18 months, with a haematopoietic stem cell transplant at 13 months (n=1).

Harmatz et al 2018 reported a sustained reduction in urinary GAG excretion from baseline to after 24 weeks of vestronidase alfa in all 12 patients. For dermatan sulfate the least squares mean change was 64.8% ($p<0.0001$[1]) and for chondroitin sulfate the least squares mean change was 70.6% ($p<0.0001$[1]). The reduction occurred within two weeks of treatment initiation in all patients.

Wang et al 2020 reported that the reductions in urinary GAG levels seen in the original blind start study (Paper 2) were sustained in the extension study (Paper 3). For dermatan sulfate the least squares mean (± standard error (SE)) reduction from blind start study baseline to week 0 of the extension study was 62% ± 5 (n=12) and at week 48 of the extension study the mean (±SE) reduction from baseline was 58% ± 7 (n=10). For chondroitin sulfate the least squares mean (±SE) reduction from blind start study baseline to week 0 of the extension study was 62% ± 8 (n=12). At week 48 of the extension study the mean (±SE) reduction from baseline was 61% ± 5 (n=10). For heparan sulfate the least squares mean (±SE) reduction from blind start study baseline to week 0 of the extension study was 51% ± 6 (n=12). At week 48 of the extension study the mean (±SE) reduction from baseline was 20% ± 10 (n=10).

The mean (± standard deviation (SD)) urinary GAG levels at different timepoints are shown in Table 1. No normal/ reference ranges or statistical analysis comparing the results at the different timepoints were reported.

Table 1: Urinary GAG levels reported by Wang et al 2020

Timepoint	Dermatan sulfate mean ± SD g GAG/g creatinine	Chondroitin sulfate mean ± SD g GAG/g creatinine	Heparan sulfate mean ± SD g GAG/g creatinine
Blind start study baseline (n=12)	1.55 ± 0.41	0.65 ± 0.25	0.0098 ± 0.0042
Extension study week 0 (n=10[2])	0.57 ± 0.23	0.23 ± 0.16	0.0044 ± 0.0023
Extension study week 48 (n=10)	0.68 ± 0.41	0.27 ± 0.18	0.0075 ± 0.0039

[1] The authors reported percentage change from baseline (the last assessment before commencement with vestronidase alfa) to after 24 weeks of treatment as a general estimating equation model including baseline value as a covariate and the week after active treatment as a fixed effect

[2] In the text this is given as n=12 for chondroitin sulfate and heparan sulfate

Extension study week 96 (n=8)	0.25 ± 0.12	0.19 ± 0.10	0.0038 ± 0.0056
Extension study week 144 (n=4[3])	0.14 ± 0.04	0.26 ± 0.08	0.0117 ± 0.0042

Three papers including a total of 13 patients reported sustained reductions in urinary GAG excretion with vestronidase alfa.

Dysmorphia

Dubot et al 2019 reported that dysmorphia had progressively improved after one year of vestronidase alfa (n=1) (no further detail reported).

One of the included papers (n=1) reported an improvement in dysmorphia after one year of vestronidase alfa.

Organ involvement

Dubot et al 2019 reported that after one year of vestronidase alfa, hepatomegaly had disappeared and spleen size had decreased but remained abnormal (n=1) (no further detail reported).

Dubot et al also reported no hepatosplenomegaly and no other organ involvement at last follow-up at four years old (no further detail reported). Vestronidase alfa was received between the ages of four and 18 months, with a haematopoietic stem cell transplant at 13 months (n=1).

One of the included papers (n=1) reported an improvement in hepatomegaly and a partial improvement in spleen size after one year of vestronidase alfa. There was no hepatosplenomegaly or other organ involvement at last follow-up at four years old (following treatment with vestronidase alfa between ages four and 18 months and a haematopoietic stem cell transplant at 13 months).

Infections

Dubot et al 2019 reported no infections after one year of vestronidase alfa (n=1) (no further detail reported).

One of the included papers (n=1) reported no infections after one year of vestronidase alfa.

Bone involvement and growth

Dubot et al 2019 reported correction of the clubfoot deformation, managed by the Ponseti method, and that after one year of vestronidase alfa other bone signs remained stable apart from a moderate spine stiffness without severe involvement (n=1) (no further detail reported).

Dubot et al also reported a stabilised growth curve on “-2 standard deviations” for age at last follow-up at four years old. Vestronidase alfa was received between the ages of four and 18 months, with a haematopoietic stem cell transplant at 13 months (n=1) (no further detail reported).

One of the included papers (n=1) reported stabilisation of bone signs after one year of vestronidase alfa and a stabilised growth curve at last follow-up at four years old (following treatment with vestronidase alfa between ages four and 18 months and a haematopoietic stem cell transplant at 13 months).

[3] Elsewhere in the study text it states that three patients completed 144 weeks of the extension study

Auditory evoked potentials

Dubot et al 2019 reported that auditory evoked potentials showed bilateral partial deafness until the age of two years (no further detail reported). Dubot et al also reported that auditory evoked potential testing was normal at last follow-up at four years old (no further detail reported). Vestronidase alfa was received between the ages of four and 18 months, with a haematopoietic stem cell transplant at 13 months (n=1).

One of the included papers (n=1) reported bilateral partial deafness at two years of age and normal auditory evoked potential testing at last follow-up at four years old (following treatment with vestronidase alfa between ages four and 18 months and a haematopoietic stem cell transplant at 13 months).

Neurological evaluation and development

Dubot et al 2019 reported that at one year of age, after eight months of vestronidase alfa, neurological evaluation was close to normal, except for global hypotonia and slight motor delay (n=1) (no further detail reported).

Dubot et al also reported normal language development without any equipment or re-education, normal psychomotor development and normal scholarship for age at last follow-up at four years old (no further detail reported). Neuropsychological tests could not be performed at four years old due to parental refusal. Vestronidase alfa was received between the ages of four and 18 months, with a haematopoietic stem cell transplant at 13 months (n=1).

One of the included papers (n=1) reported that neurological examination was close to normal at one year old, after eight months of vestronidase alfa. Language, psychomotor development and scholarship were normal at last follow-up at four years old (following treatment with vestronidase alfa between ages four and 18 months and a haematopoietic stem cell transplant at 13 months).

Multi-domain response

Harmatz et al 2018 reported that ten of the 12 patients had a clinically meaningful improvement in at least one of the six multi-domain responder index (MDRI)[4] domains. When imputation[5] was used for missing results the overall mean (±SD) change from baseline to after 24 weeks of vestronidase alfa for the MDRI was +0.5 (±0.8) (p=0.0527). When using only observed results (i.e. no imputation) the overall mean (±SD) change was +0.6 (±0.67) (p=0.0116).

Harmatz et al 2018 also reported the results for each of the six clinical domains of the MDRI:

- Six-minute walk test: for the nine of the 12 patients with results available, the least squares mean change (SE) from baseline to after 24 weeks of vestronidase alfa was 20.8 metres (16.75) (p=0.2137[6]). The authors reported that three patients had an

[4] The multi-domain responder index (MDRI) consisted of six clinical domains: the six-minute walk test, forced vital capacity, shoulder flexion, visual acuity and fine motor and gross motor proficiency assessed using the Bruininks-Oseretsy Test of Motor Proficiency. Each domain score was calculated based on the minimally important difference which was pre-defined based on literature reports and prior studies. Non-assessable domains (for example if the patient was unable to walk) were scored as 0. The domain scores were -1 for decline, 0 for no change and +1 for improvement. The domain scores were summed to create the MDRI score

[5] If a domain was missing (assessable but not performed) at 24-weeks treatment, the domain score at 32-weeks treatment was used for imputation. If the domain score at 32-weeks was missing the score at 16-weeks treatment was used. MDRI imputation was applied to two of the 12 patients (one domain for one patient and four domains for one patient)

[6] General estimating equation model

improvement that exceeded the predefined minimally important difference (≥23 metres and ≥10% change from baseline)

- Forced vital capacity: The authors reported that nine of the 12 patients could not perform this test at baseline so no statistical analysis was performed. The authors reported that one patient had improved breathing and less need for nocturnal oxygen support based on parental report. Results, displayed graphically, suggest that one patient had 'worsened' forced vital capacity compared to baseline (based on the results for the predefined MDRI minimally important difference analysis[7]) and one patient had no change (figures not stated)
- Shoulder flexion: The authors stated that patients had little shoulder flexion restriction at baseline (reported as "mean for tighter shoulder = 139°"; and stated as "close to normal range of around 160°") and therefore that no appreciative change from baseline in "mean flexion and extension for shoulder range of motion by goniometry" was observed. Results, displayed graphically, suggest that 11 patients had no change and one patient 'worsened' compared to baseline (based on the results for the predefined MDRI minimally important difference analysis[8]) (figures not stated)
- Visual acuity (uncorrected): for the seven of the 12 patients with results available, the least squares mean change (SE) from baseline to after 24 weeks of vestronidase alfa was 1.0 lines (0.63) (p=0.1140) for the left eye and 0.9 lines (0.51) (p=0.0906) for the right eye. The authors reported that four patients showed an uncorrected improvement of at least two lines on the Snellen eye chart in one or both eyes. Results, displayed graphically, suggest that one patient had an improvement meeting the predefined minimally important difference (three lines corrected, both eyes)
- Fine motor and gross motor proficiency: The authors stated that the mean change from baseline was minimal and not statistically significant (figures not reported). Results, displayed graphically, suggest that two patients showed an improvement meeting the predefined minimally important difference in fine motor proficiency from baseline (fine motor precision change of 0.72 and manual dexterity change of 1.47), nine patients had no change and one patient was not assessable. For gross motor proficiency, three patients showed an improvement meeting the predefined minimally important difference from baseline (balance 0.57 and running speed and agility 0.59), two patients had no change, one patient 'worsened' (based on the results for the predefined MDRI minimally important difference analysis) and six patients were not assessable

Wang et al 2020 reported that there were sustained benefits in overall MDRI score in the extension study (Paper 3). At the start of the extension study (week 0) (n=12) the mean ± SD score was +0.3 ± 0.8, at week 24 (n=11) it was +0.7 ± 1.0 and at week 48 (n=11) it was +0.9 ± 1.3.

After week 48 of the extension study the MDRI score only included four of the six clinical domains as fine motor and gross motor proficiency were no longer assessed. At week 96 (n=8) the mean ± SD MDRI score was +0.5 ± 0.9 and at week 144 (n=3) the mean ± SD score was +0.3 ± 0.6.

Wang et al 2020 also reported the results for each of the six clinical domains of the MDRI:

- Six-minute walk test: The mean ± SD distance walked was 259m ± 186 (or 38% ± 25% predicted distance walked for age and sex) at baseline in the blind start study (n=9), 319m ± 202 (or 45% ± 28%) at week 0 of the extension study (n=7), 308 ± 174m (or 44% ± 23%) at week 48 (n=8) and 349m ± 168 (or 50% ± 22%) at week 96 (n=5). The authors reported that four of seven patients achieved a clinically meaningful difference (≥23 metres and ≥10% change from baseline) in the six-minute walk test at week 24 and/or

[7] The pre-specified minimally important difference was 5% absolute change or 10% relative change from baseline in forced vital capacity % pred.

[8] The pre-specified minimally important difference was 20% change of passive shoulder range of motion

week 48 of the extension study. One patient showed a “reduction” in the six-minute walk test at week 48 of the extension study (no figures stated)[9]

- Forced vital capacity: Two patients completed this test and were reported to have shown little change from baseline (percent predicted forced vital capacity: blind start baseline 88.0% and 81.0%; week 104 86% and 84%)
- Shoulder flexion: The authors reported that this showed “no appreciable worsening”. The mean ± SD minimum range of motion was 138.7° ± 13.9 at baseline in the blind-start study (n=12), 139.6° ± 16.1 at week 48 (n=11) and 126.7° ± 7.6 at week 144 (n=3)
- Visual acuity (uncorrected): The authors stated that these scores remained stable. The mean ± SE change from baseline in the blind-start study to week 48 in the extension study was 1.3 lines ± 0.76 for the left eye and 1.2 lines ± 0.83 for the right eye
- Fine motor and gross motor proficiency: The authors stated that these scores remained stable. The mean ± SE change from baseline in the blind start study to week 48 in the extension study for the two components of fine motor proficiency were 0.3 ± 0.47 for fine motor precision (n=7) and -0.8 ± 0.53 for manual dexterity (n=8). For the two components of gross motor proficiency the mean ± SE change was 0.2 ± 0.48 for balance (n=6) and 0.3 ± 0.21 for running speed and agility (n=6).

One of the included papers reported that ten of the 12 patients had a clinically meaningful improvement in at least one of the six MDRI domains (the six-minute walk test, forced vital capacity, shoulder flexion, visual acuity and fine motor and gross motor proficiency). A second included paper, reporting an extension to this study, found that improvements in overall MDRI score were sustained at up to 144 weeks follow-up.

[9] The authors stated that this may have been due to challenges with comprehension as the patient had developmental delay and showed variable improvement in this test throughout the study

Fatigue

Harmatz et al 2018 reported that nine of 12 patients had an improved fatigue score[10] from baseline at some point during the study. There was no statistically significant difference in the least squares mean change (±SE) from baseline to after 24 weeks of vestronidase alfa: 3.4 (±2.64) (p=0.1953).

Wang et al 2020 reported that improvements in fatigue scores observed in the blind start study (Paper 2) were sustained through the extension study (Paper 3). The mean ± SD fatigue score was 64.5 ± 15.9 at baseline in the blind-start study (n=12), 71.3 ± 15.1 at week 0 of the extension study (n=12), 72.1 ± 14.2 at week 24 (n not stated), 70.9 ± 19.7 at week 48 (n=11), 72.0 ± 16.8 at week 96 (n=9) and 71.5 ± 11.2 at week 144 of the extension study (n=4). The authors reported a clinically meaningful improvement in four patients for at least one timepoint (≥10 point change in total fatigue score from baseline).

One of the included papers reported an improved fatigue score in nine of 12 patients at some point during the study. A second included paper, reporting an extension to this study, found that improvements in fatigue score were sustained at up to 144 weeks follow-up. In the second paper the improvement was described as clinically meaningful in four of the 12 patients for at least one follow-up timepoint.

Modified multi-domain response with fatigue

Harmatz et al 2018 reported a modified MDRI score with fatigue added to the existing six clinical domains. When imputation was used for missing results the mean (±SD) improvement after 24 weeks of vestronidase alfa was +0.8[11] (±1.14) (p=0.0433). When using only observed results (i.e. no imputation) the mean (±SD) improvement was +0.8 (±0.94) (p=0.0105).

One of the included papers (n=12) reported an improvement in a modified MDRI score with fatigue added after 24 weeks of vestronidase alfa.

Safety

Dubot et al 2019 reported that after one year, vestronidase alfa was well tolerated and no adverse effects were reported (n=1) (no further detail reported).

Harmatz et al 2018 (n=12) reported that treatment with vestronidase alfa was not associated with any unexpected risks. There were no deaths during the study and no patients discontinued or missed infusions due to an adverse event. The authors reported that two patients had one hypersensitivity infusion-associated reaction each (0.9% of the 215 total infusions for all patients). One patient had a serious treatment-related anaphylactoid reaction during an infusion. There were no recurrent hypersensitivity events.

The most common adverse events with placebo and vestronidase alfa were reported in two ways. The incidence regardless of causality and incidence by exposure adjusted rates. The authors reported no statistically significant differences in exposure-adjusted incidence rates of treatment-emergent adverse events[12].

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[10] Fatigue was assessed using the Pediatric Quality of Life Inventory™-Multidimensional Fatigue Scale. This has three dimensions, general, sleep/rest and cognitive fatigue with total fatigue as the average of the three dimensions. Scores range from 0 to 100 with higher scores indicating less fatigue. The pre-specified minimally important difference was an improvement for ≥10 points increase from baseline in fatigue total score or a worsening for ≥10 points reduction from baseline in fatigue total score

[11] Each domain score (-1 for decline, 0 for no change, +1 for improvement) was calculated based on the predefined minimally important difference and summed for the MDRI score. For the modified MDRI score fatigue was added to the original six clinical domains

[12] Defined as the total number of occurrences of the treatment-emergent adverse event divided by the total amount of time subjects participated in the analysis group phase

Table 2: Adverse events from Harmatz et al 2018

Adverse event	Incidence regardless of causality		Incidence by exposure adjusted rates	
	Placebo (n=9) n (%)	Vestronidase alfa (n=12) n (%)	Placebo (subject-years 2.7) number (rate)	Vestronidase alfa (subject-years 8.3) number (rate)
Upper respiratory tract infection	3 (33.3)	5 (41.7)	3 (1.1)	6 (0.7)
Pain in extremity	3 (33.3)	4 (33.3)	3 (1.1)	5 (0.6)
Infusion site extravasation	1 (11.1)	4 (33.3)	1 (0.4)	4 (0.5)
Cough	2 (22.2)	3 (25.0)	2 (0.7)	3 (0.4)
Vomiting	2 (22.2)	3 (25.0)	3 (1.1)	3 (0.4)
Rash	1 (11.1)	3 (25.0)	2 (0.7)	3 (0.4)
Diarrhoea	0 (0.0)	3 (25.0)	0 (0.0)	3 (0.4)
Anaphylactoid reaction	0 (0.0)	2 (16.7)	0 (0.0)	2 (0.2)

Harmatz et al 2018 reported that seven of the 12 patients tested positive for anti-drug antibodies, with six of the seven described as treatment emergent. The authors reported no association between antibody formation and immune-mediated adverse events.

Wang et al 2020 reported that all 12 patients who received vestronidase alfa for between one and 144 weeks in an extension study experienced an adverse event. In nine patients (75%) this was considered a treatment-related adverse event. Three of the 12 patients (25%) experienced serious adverse events[13]. In one patient (8.3%) the serious adverse events (bronchospasm and urticaria) were considered treatment-related. Seven patients (58%) had an infusion-associated reaction which were described as mild to moderate. No patients died or discontinued vestronidase alfa due to an adverse event. The authors stated that there were no life-threatening (Grade 4) adverse events.

The most commonly reported adverse events are presented in Table 3.

[13] This figure is taken from the table of adverse events in the study. In the text it states that four patients had serious adverse events

Table 3: Adverse events from Wang et al 2020

Adverse event	n (%)
Upper respiratory tract infection	7 (58.3)
Infusion site extravasation	5 (41.7)
Urticaria	5 (41.7)
Cough	4 (33.3)
Vomiting	4 (33.3)
Gastro-oesophageal reflux disease	3 (25.0)
Nasal congestion	3 (25.0)
Rhinitis	3 (25.0)
Arthralgia	2 (16.7)
Bronchospasm	2 (16.7)
Conjunctivitis allergic	2 (16.7)
Diarrhoea	2 (16.7)
Ear infection	2 (16.7)
Ear pain	2 (16.7)
Head injury	2 (16.7)
Headache	2 (16.7)
Infusion site swelling	2 (16.7)
Lethargy	2 (16.7)
Ligament sprain	2 (16.7)
Nasopharyngitis	2 (16.7)
Nausea	2 (16.7)
Oedema peripheral	2 (16.7)
Otitis media acute	2 (16.7)
Pain in extremity	2 (16.7)
Pollakiuria	2 (16.7)
Pyrexia	2 (16.7)
Rash	2 (16.7)
Rash papular	2 (16.7)
Rhinitis allergic	2 (16.7)
Rhinorrhoea	2 (16.7)
Skin abrasion	2 (16.7)
Upper respiratory tract congestion	2 (16.7)

Wang et al 2020 reported that of 11 (of 12) patients who tested positive for anti-drug antibodies at any point during the original or extension study, seven tested positive for neutralising antibodies.

One of the included papers (n=12) reported that all patients experienced an adverse effect during treatment with vestronidase alfa, with 75% considered to be treatment-related. Two of the included papers with a total of 12 patients each reported one treatment-related serious adverse event (not life-threatening). The third included paper reported no adverse effects in one patient.

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