## Additional file

**S1** Urinary glycosaminoglycan (uGAG) levels over time

| Patient | uGAG (mg/g creatinine) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline | Months after initiation of ERT | | | | | | | | |
| | | 6 | 12 | 18 | 24 | 30 | 36 | 48 | 54 | 72 |
| 1 | 123.5 | | 74.0 | | 5.0 | | | | | |
| 2 | 112.8 | 98.3 | 38.0 | | 7.7 | | 19.3 | | | 12.4 |
| 3 | 65.2 | 29.0 | 27.9 | 7.3 | 1.8 | | | | | |
| 4 | 132.8 | 112.5 | 32.5 | 24.0 | 12.6 | 6.7 | 8.9 | | | |
| 5 | 81.6 | 24.1 | 10.8 | 28.3 | 31.5 | | | | | |
| 6 | 154.3 | 98.6 | 76.8 | 39.3 | 11.7 | 9.6 | 10.3 | | | |
| 7 | 124.4 | 111.6 | 83.6 | 56.0 | | | | 32.0 | 14.7 | |
| 8 | 24.3 | 8.4 | 27.0 | 25.0 | 7.0 | 6.7 | 1.8 | | | 2.0 |
| 9 | 307.7 | 86.0 | 224.0 | 42.0 | 32.0 | 115.7 | 21.0 | | | 16.0 |
| 10 | 128.8 | 78.6 | | 54.7 | 32.6 | | 42.5 | | 21.7 | |
| 11 | 201.1 | | 120.0 | | 47.0 | | | | | |
| 12 | 28.3 | | | | 11.5 | | 15.5 | 9.7 | | |
| 13 | 63.2 | 38.0 | 29.1 | | 29.0 | | 17.4 | | | |
| 14 | 32.3 | | | 4.2 | 2.2 | | | | | |

**S2** Height and mucopolysaccharidosis VI-specific height percentile (based on Quartel et al, 2015 [1]) before treatment initiation and follow-up (boys and girls)

| **Case** | **Height at initiation of ERT** | | **Height at last follow-up** | |
|---|---|---|---|---|
| | **Height, cm** | **Percentile** | **Height, cm** | **Percentile** |
| **1** | 90.00 | P75-90 | 94.00 | P25-50 |
| **2** | 87.00 | P25-50 | 102.00 | P50-75 |
| **3** | 109.30 | >P95 | 112.00 | P90-95 |
| **4** | 96.00 | P50-75 | 104.00 | P50-75 |
| **5** | 97.00 | P50-75 | 99.00 | P50-75 |
| **6** | 90.00 | P25-50 | 94.80 | P25-50 |
| **7** | 103.00 | P75-90 | 107.00 | P50-75 |
| **8** | 112.00 | P90-95 | 115.00 | P75-90 |
| **9** | 99.00 | P25-50 | 102.00 | P25-50 |
| **10** | 96.00 | P25-50 | 102.00 | P25-50 |
| **11** | 116.00 | P75-90 | 120.00 | P50-75 |
| **12** | 149.00 | >P95 | 152.00 | P75-90 |
| **13** | 145.00 | P90-95 | 145.00 | P75-90 |
| **14** | 147.40 | P75-90 | 148.40 | (P75-90)[a] |

[a]Data for 18 years of age (patients was 18.2 years of age, which is outside the reference curve)

1. Quartel A, Hendriksz CJ, Parini R, Graham S, Lin P, Harmatz P. Growth charts for individuals with mucopolysaccharidosis VI (Maroteaux-Lamy Syndrome). JIMD Rep. 2015;18:1-11.

**S3** Cardiac echocardiography findings at initiation of enzyme replacement therapy (baseline) and at last follow-up. AR: aortic regurgitation, MR: mitral regurgitation, TR: tricuspid regurgitation. Green indicates normal mitral/aortic valves, orange indicates abnormal valves

| Case | Mitral valve | | Aortic valve | | Other findings | |
|---|---|---|---|---|---|---|
| | **Baseline** | **Follow-up** | **Baseline** | **Follow-up** | **Baseline** | **Follow-up** |
| 1 | Normal | Normal | Normal | Normal | - | - |
| 2 | 2nd degree MR | 2nd degree MR | Normal | 2nd degree AR | Minimal TR, ventricular extrasystole | - |
| 3 | Mild thickening | Mild thickening | Normal | Mild thickening | - | - |
| 4 | 2nd degree MR | 2nd degree MR | Minimal AR | 2nd degree AR | - | - |
| 5 | Mild thickening | 2nd degree MR | Normal | Normal | - | - |
| 6 | 2nd degree MR | 2nd degree MR | Minimal AR | Minimal AR | Minimal TR | Minimal TR |
| 7 | Mild MR | 2nd degree MR | Normal | Mild AR | Intraventricular septum hypertrophy | Mild TR |
| 8 | 2nd degree MR | 2nd degree MR | 1st degree AR | 2nd degree AR | - | - |
| 9 | Minimal MR | 2nd degree MR | Normal | 3rd degree AR | Intraventricular septum hypertrophy, minimal TR | Minimal TR |
| 10 | 1st degree MR | 2nd degree MR | Normal | Normal | - | - |
| 11 | 2nd degree MR | 2nd degree MR | 2nd degree AR | 3rd degree AR | - | - |
| 12 | 2nd degree MR | 2nd degree MR | Normal | Normal | - | - |
| 13 | 3rd degree MR | 2nd degree MR | 2nd degree AR | 2nd degree AR | Minimal pericardial effusion | - |
| 14 | 2nd degree MR | 2nd degree MR | Normal | 2nd degree AR | _ | _ |

**S4** Cranial and spinal magnetic resonance (MRI) outcomes at initiation of enzyme replacement therapy at baseline (BL) and follow-up (FU).

NA: not available; WM: white matter

| Case | | Cranial MRI | Spinal MRI | Spinal cord compression |
|---|---|---|---|---|
| **1** | BL | - | - | - |
| | FU | - | - | - |
| **2** | BL | Increased perivascular space, WM changes | Mild cervical flattening and narrowing | - |
| | FU | No change | - | - |
| **3** | BL | - | - | - |
| | FU | - | - | - |
| **4** | BL | - | - | - |
| | FU | NA[a] | NA[a] | - |
| **5** | BL | - | - | - |
| | FU | - | - | - |
| **6** | BL | Increased perivascular space | - | - |
| | FU | Increased perivascular space, narrow foramen magnum | Narrow foramen magnum and C1 | Mild compression |
| **7** | BL | Increased perivascular space | Mild cervical flattening | - |
| | FU | Increased perivascular space | - | - |
| **8** | BL | Asymmetric enlargement of lateral ventricles | Flattening of vertebral bodies, wedging of cervical vertebrae | - |
| | FU | Asymmetric enlargement of lateral ventricles | Kyphosis, schmorl nodules at vertebral corpus end plate, flattened vertebrae | - |
| **9** | BL | Arachnoid cyst | - | - |
| | FU | Arachnoid cyst, enlarged lateral & 3rd ventricle, WM edema | Narrowing of spinal canal at foramen magnum and C1 | Obvious compression |
| **10** | BL | Increased periventricular space, enlarged ventricles, narrow foramen magnum | Narrow foramen magnum | No symptoms |
| | FU | Increased periventricular space, enlarged ventricles, narrow foramen magnum, ventriculoperitoneal shunt | Narrow foramen magnum | No symptoms |
| **11** | BL | Periventricular leukodystrophy | - | - |
| | FU | Periventricular leukodystrophy | Mild narrowing of foramen magnum | - |
| **12** | BL | Signal increase in occipital in calvarial bones | Narrow spinal canal at C1-C2 | No symptoms |

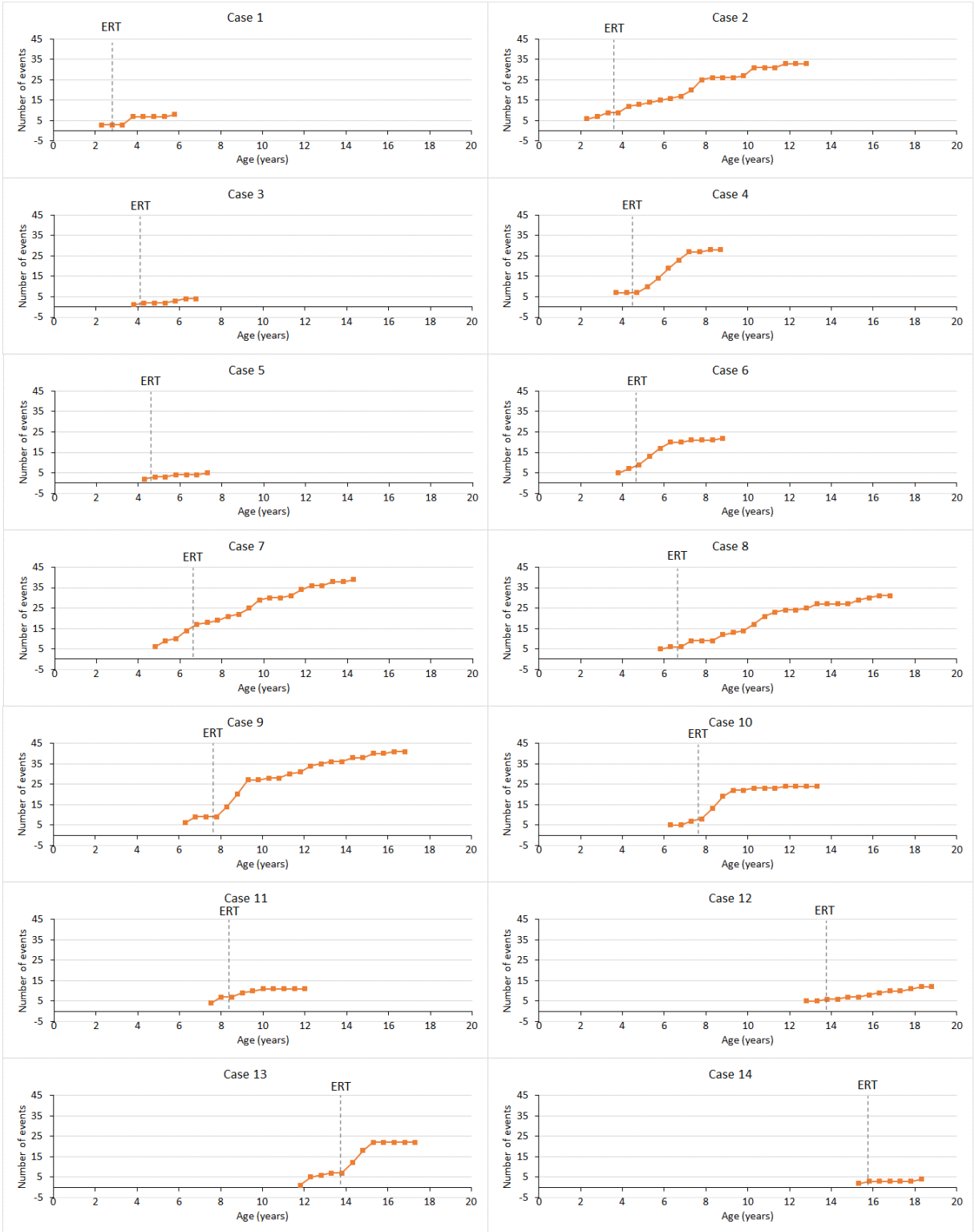
| | | | | |
|---|---|---|---|---|
| | FU | Prominence in the prepontine system, signal increase in occipital calvarial bones | Narrow spinal canal at C1-C7 | No symptoms |
| **13** | BL | Tetraventricular hydrocephaly, increased periventricular space, narrow foramen magnum | Narrow foramen magnum | No symptoms |
| | FU | Tetraventricular hydrocephaly, increased periventricular space, narrow foramen magnum, flattened C1-C2 | Narrow foramen magnum | No symptoms |
| **14** | BL | Widening of Virchow Robin space | Narrow spinal canal | No symptoms |
| | FU | Widening of Virchow Robin space | Narrow spinal canal | No symptoms |

[a]MRI could not be performed because of cochlear implants

**S5** Urinary incontinence at initiation of enzyme replacement therapy (baseline) and at last follow-up

| Case | Age at initiation of ERT | Urinary incontinence | |
|---|---|---|---|
| | | **Baseline** | **Follow-up** |
| **1** | 2.8 | Sometimes | Never |
| **2** | 3.8 | Always | Rarely |
| **3** | 4.3 | Never | Never |
| **4** | 4.7 | Rarely | Rarely |
| **5** | 4.8 | Never | Never |
| **6** | 4.8 | Sometimes | Rarely |
| **7** | 5.8 | Never | Never |
| **8** | 6.8 | Sometimes | Never |
| **9** | 7.8 | Rarely | Sometimes |
| **10** | 7.8 | Never | Never |
| **11** | 8.5 | Rarely | Always |
| **12** | 13.8 | Never | Never |
| **13** | 13.8 | Never | Never |
| **14** | 15.8 | Never | Never |

**S6** Cumulative number of events by age before and after initiation of ERT. Individual patient data



**S7** Summary of event-based outcomes

*Severe upper and lower respiratory tract infections*

All patients, except cases 3, 5, and 14, had recurrent upper respiratory tract infections (ranging from two to four) before treatment initiation. In most cases, the frequency of infections dropped during follow-up, with only cases 5 and 14 reporting infections in the last 6 months of follow-up.

*Ophthalmologic*

Three patients had eyeglasses before ERT was started (cases 3, 4, 11); the remaining patients, except cases 5 and 14, started wearing eyeglasses during follow-up. Case 13 had eye pain and started taking glaucoma medication within the first year of ERT. Cases 1 and 11 were reported to have cataract around 3 years and 1.5 years after treatment initiation, respectively.

*Respiratory*

Sleep apnea (snoring) and/or requirement of $O_2$ therapy was reported for six cases before initiation of ERT (2, 6, 8, 10, 12 and 14). Sleep apnea was reported at least once after initiation of ERT in three out of six patients (2, 8 and 12), but was no longer reported after 0 to 1.5 years of treatment in the three others. Five patients (1, 4, 7, 9 and 13) developed sleep apnea or required $O_2$ therapy after initiation of treatment.

*Upper airway*

All patients, except case 3, had an adenotonsillectomy or adenoidectomy before initiation of ERT (Supplementary table S2). Cases 2, 7, and 8 had another adenoidectomy around 5 years after initiation of ERT. Case 9 had a tracheostomy around 1 year after treatment initiation.

*Hearing*

Case 4 had a cochlear implant before initiation of ERT. Five patients (cases 4, 6, 8, 10, 13) had ear tube insertions during follow-up.

*Psychiatric*

Seven patients (cases 3, 5, 6, 7, 9, 10, and 14) reported depression before initiation of ERT. Ten patients (cases 1, 2, 4, 6, 7, 8, 9, 10, 11, and 13) had periods of depression during follow-up.

*Sleep*

Ten patients (cases 2, 4, 5, 6, 7, 8, 9, 10, 11, 12) reported reduced quality of sleep (including frequent awakenings/interrupted sleep, sweating, and daytime sleeping) before ERT was initiated. Sleep problems persisted during follow-up in cases 6, 7, 9, but largely resolved in the other patients.

*Cardiac*

At baseline, case 13 was treated with an angiotensin-conversion-enzyme (ACE) inhibitor and case 2 was diagnosed with ventricular extrasystole. Eight patients were received ACE inhibitors (cases 2, 4, 5, 7, 9, 10, 11 and 13) during follow-up. Case 4 was diagnosed with minimal pericardial effusion in the first year after treatment initiation.

*Mobility*

No mobility events were reported before initiation of ERT. Case 7 started using a walker around 3.5 to 4 years after initiation of ERT; case 9 became immobile after around 1.5 years of treatment. Botox injections every 6 months were started to treat spasticity in cases 1 and 11 shortly after initiation of ERT.

*Abdominal*

Case 13 had an umbilical hernia repair before starting ERT. None of the other patients developed umbilical hernias during follow-up.

*Pain*

Cases 7 and 9 reported leg pain before ERT was started, and intermittently during follow-up. After treatment initiation, case 2 intermittently reported chest pain, case 4 started reporting elbow pain shortly after treatment initiation up to 3 years follow-up, case 8 reported vertebral

pain in the first year on ERT and again after 5 years of treatment until last follow-up, and case 9 reported headaches in the first year of ERT. Case 13 reported eye pain in the first year of treatment.

*Neurological*

Case 9 developed spinal cord compression in the first year after treatment initiation. Case 4 was diagnosed with carpal tunnel syndrome in the first year after treatment initiation.