

## **SUPPLEMENTARY MATERIALS**

### **Long-term outcomes of eladocogene exuparvovec compared with standard of care in aromatic L amino acid decarboxylase (AADC) deficiency: A modelling study**

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## S1: Definition of motor milestones

The achievement of a motor milestone was assessed using the following definitions:

- i) *Full-head control*: The patient achieves a score of at least 1 on item #10 of the stationary (gross motor) subscale of PDMS-2
- ii) *Sitting unassisted*: The patient achieves a score of at least 1 on item #14 of the stationary (gross motor) subscale of PDMS-2
- iii) *Stepping/standing with support*: The patient achieves a score of at least 1 on item #28 of the locomotion (gross motor) subscale of PDMS-2
- iv) *Walking with assistance*: The patient achieves a score of at least 1 on item #34 of the locomotion (gross motor) subscale of PDMS-2.

*Table S1 Population characteristics in the pivotal trials for eladocogene exuparvovec at baseline  
(Source: Individual participant data)*

| Parameters                                    | N=21<br>(1.8x10 <sup>11</sup><br>vg) | N=30<br>(All<br>patients) | AADC-<br>1601 | AADC-010    | AADC-011 (split by<br>dosage) |                            |
|-----------------------------------------------|--------------------------------------|---------------------------|---------------|-------------|-------------------------------|----------------------------|
|                                               |                                      |                           |               |             | 1.8x10 <sup>11</sup><br>vg    | 2.4x10 <sup>11</sup><br>vg |
| N                                             | 21                                   | 30                        | 8             | 10          | 3                             | 9                          |
| Median duration<br>of follow-up<br>(months)*  | 75.7                                 | 60.9                      | 124.7         | 73.9        | 61.6                          | 29.7                       |
| <b>Demographic characteristics</b>            |                                      |                           |               |             |                               |                            |
| Age (months),<br>mean (SD)                    | 55.2 (25.9)                          | 45.7 (26.2)               | 58.8 (24.8)   | 52.5 (30.8) | 55.0 (13.2)                   | 23.3 (3.3)                 |
| Age at<br>diagnosis<br>(months),<br>Mean (SD) | 13.6 (8.4)                           | 12.9 (8.1)                | 15.9 (9.7) *  | 11.4 (7.0)  | 15.3 (11.0)                   | 11.3 (7.4)                 |
| Gender<br>(female),<br>N (%)                  | 11 (52.4%)                           | 14 (46.7%)                | 5 (62.5%)     | 5 (50.0%)   | 1 (33.3%)                     | 3 (33.3%)                  |
| Mutation                                      |                                      |                           |               |             |                               |                            |
| Homozygous<br>founder<br>mutation             | 14 (66.7%)                           | 18 (60.0%)                | 7 (87.5%)     | 6 (60.0%)   | 1 (33.3%)                     | 4 (44.4%)                  |
| Age at symptom onset, n (%)                   |                                      |                           |               |             |                               |                            |
| ≤ 6 months                                    | 12 (57.1%)                           | 19 (63.3%)                | 2 (25.0%)     | 9 (90.0%)   | 1 (33.3%)                     | 7 (77.8%)                  |
| ≤ 12 months                                   | 3 (14.3%)                            | 5 (16.7%)                 | 0 (0.0%)      | 1 (10.0%)   | 2 (66.7%)                     | 2 (22.2%)                  |
| > 12 months                                   | 5 (23.8%)                            | 5 (16.7%)                 | 5 (62.5%)     | 0 (0.0%)    | 0 (0.0%)                      | 0 (0.0%)                   |
| Unknown                                       | 1 (4.8%)                             | 1 (3.3%)                  | 1 (12.5%)     | 0 (0.0%)    | 0 (0.0%)                      | 0 (0.0%)                   |
| Age at gene therapy, n (%)                    |                                      |                           |               |             |                               |                            |
| < 2 years                                     | 1 (4.8%)                             | 7 (23.3%)                 | 0 (0.0%)      | 1 (10.0%)   | 0 (0.0%)                      | 6 (66.7%)                  |
| 2 to <6 years                                 | 13 (61.9%)                           | 16 (53.3%)                | 5 (62.5%)     | 5 (50.0%)   | 3 (100.0%)                    | 3 (33.3%)                  |
| 6 to <12 years                                | 7 (33.3%)                            | 7 (23.3%)                 | 3 (37.5%)     | 4 (40.0%)   | 0 (0.0%)                      | 0 (0.0%)                   |

| Disease characteristics |                                                             |
|-------------------------|-------------------------------------------------------------|
| Full-head control       | All patients in the trial had no motor function at baseline |
| Sitting unassisted      |                                                             |
| Standing with support   |                                                             |
| Walking with assistance |                                                             |

\* Based on time of last visit

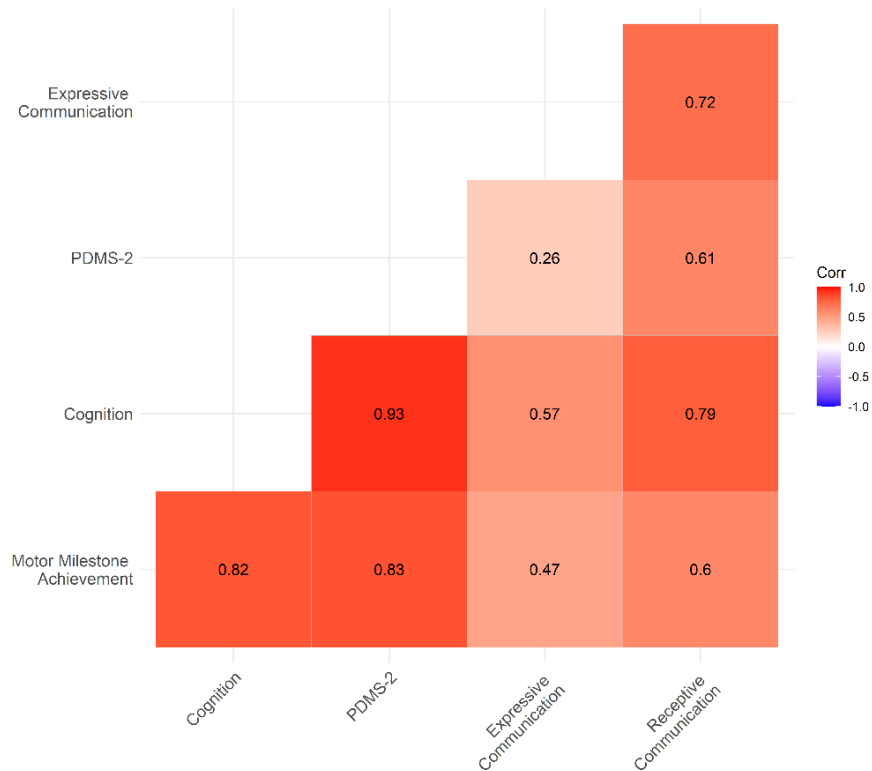


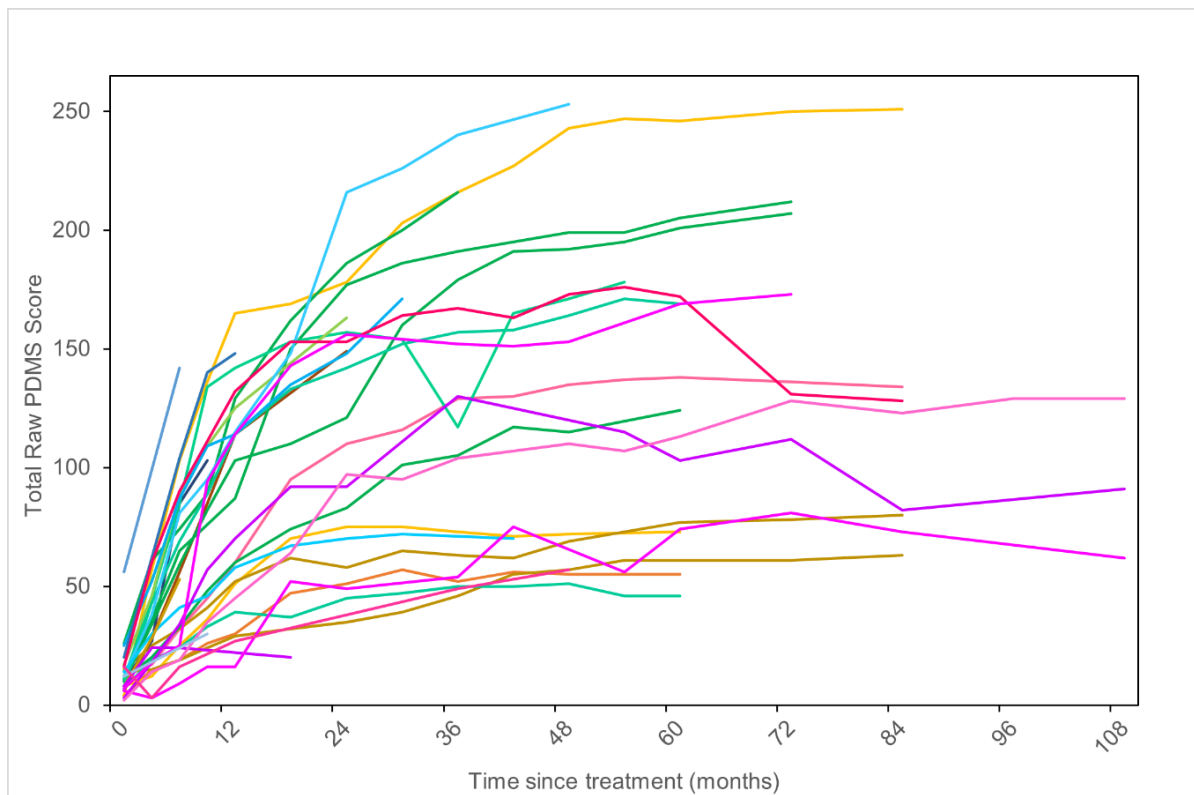
Figure S1. Correlation coefficients between the motor milestones, PDMS-2 score, and the receptive communication, expressive communication, and cognition components of the Bayley-III score for the n=30 population

Table S2. BSC basket composition (32)

|                         | No-motor function | Full-head control | Sitting unassisted | Standing with support | Walking with assistance |
|-------------------------|-------------------|-------------------|--------------------|-----------------------|-------------------------|
| Dopamine agonists       | 89%               | 89%               | 75%                | 86%                   | 86%                     |
| MAO inhibitors          | 67%               | 67%               | 50%                | 86%                   | 86%                     |
| Vitamin B6              | 89%               | 89%               | 75%                | 86%                   | 86%                     |
| Anticholinergic agents  | 11%               | 11%               | 0%                 | 0%                    | 0%                      |
| Benzodiazepines         | 33%               | 33%               | 0%                 | 0%                    | 0%                      |
| Melatonin               | 44%               | 44%               | 0%                 | 30%                   | 30%                     |
| Clonidine               | 0%                | 0%                | 0%                 | 0%                    | 0%                      |
| L-Dopa                  | 20%               | 22%               | 25%                | 43%                   | 43%                     |
| Folic acid (vitamin B9) | 67%               | 67%               | 25%                | 14%                   | 14%                     |

|                    |     |     |     |     |     |
|--------------------|-----|-----|-----|-----|-----|
| Dietary supplement | 11% | 11% | 0%  | 14% | 14% |
| Vitamin D          | 20% | 20% | 10% | 0%  | 0%  |

Key: MAO, monoamine oxidase



The different colours represent different patients

Figure S2. The relationship between the total raw PDMS-2 score and time since treatment with eladocagene exuparvovec (n=30)

Table S3. Coefficients and goodness of fit statistics for the survival analysis using data from Brooks et al. (2004) (23)

| Motor milestone state          |                  | Coefficients<br>(95% confidence interval)       | AIC           | BIC           |
|--------------------------------|------------------|-------------------------------------------------|---------------|---------------|
| <b>No-motor function</b>       |                  |                                                 |               |               |
| Exponential                    | Rate             | 0.0483 (0.036, 0.061)                           | -12.22        | -12.32        |
| Weibull                        | Scale<br>Shape   | 17.736 (17.275, 22.196)<br>1.477 (1.001, 1.952) | -17.98        | -18.14        |
| Gompertz                       | Rate<br>Shape    | 0.031 (0.010, 0.053)<br>0.041 (-0.015, 0.097)   | -14.11        | -14.27        |
| Log Normal                     | Logmean<br>Sdlog | 2.689 (2.615, 2.762)<br>0.775 (0.642, 0.908)    | <b>-27.14</b> | <b>-27.30</b> |
| Loglogistic                    | Shape<br>Scale   | 2.136 (1.697, 2.575)<br>14.732 (13.48, 15.98)   | -25.05        | -25.22        |
| <b>Full-head control</b>       |                  |                                                 |               |               |
| Exponential                    | Rate             | 0.022 (0.017, 0.027)                            | -17.40        | -17.51        |
| Weibull                        | Scale<br>Shape   | 34.467 (31.707, 37.226)<br>1.625 (1.360, 1.890) | -32.69        | -32.85        |
| Loglogistic                    | Shape<br>Scale   | 1.981 (1.736, 2.227)<br>27.556 (26.269, 28.843) | <b>-36.72</b> | <b>-36.88</b> |
| <b>Sitting unassisted</b>      |                  |                                                 |               |               |
| Exponential                    | Rate             | 0.014 (0.011, 0.018)                            | -18.69        | -18.79        |
| Weibull                        | Scale<br>Shape   | 41.378 (38.203, 44.553)<br>1.876 (1.624, 2.128) | <b>-39.10</b> | <b>-39.26</b> |
| Loglogistic                    | Shape<br>Scale   | 2.147 (1.788, 2.506)<br>35.133 (32.421, 37.845) | -36.16        | -36.32        |
| <b>Standing with support</b>   |                  |                                                 |               |               |
| Exponential                    | Rate             | 0.004 (0.003, 0.005)                            | -34.98        | -35.09        |
| Weibull                        | Scale<br>Shape   | 86.173 (77.181, 96.165)<br>1.792 (1.641, 1.944) | -61.04        | -61.20        |
| Loglogistic                    | Shape<br>Scale   | 1.870 (1.718, 2.022)<br>79.310 (71.804, 86.816) | <b>-61.56</b> | <b>-61.72</b> |
| <b>Walking with assistance</b> |                  |                                                 |               |               |
| Exponential                    | Rate             | 0.002 (0.001, 0.003)                            | -34.73        | -34.83        |
| Weibull                        | Scale<br>Shape   | 62.999 (56.162, 69.837)<br>3.305 (2.869, 3.741) | <b>-63.18</b> | <b>-63.34</b> |
| Loglogistic                    | Shape<br>Scale   | 3.384 (2.913, 3.853)<br>61.152 (54.394, 67.911) | -62.47        | -62.63        |

Note: The following models did not converge: No motor function – Gamma; Full head control – Gompertz, log Normal, Gamma; Sitting unassisted – Gompertz, Log-normal; Gamma; Standing with support – Gompertz, log Normal, Gamma; Walking with assistance – Gompertz, log Normal, Gamma

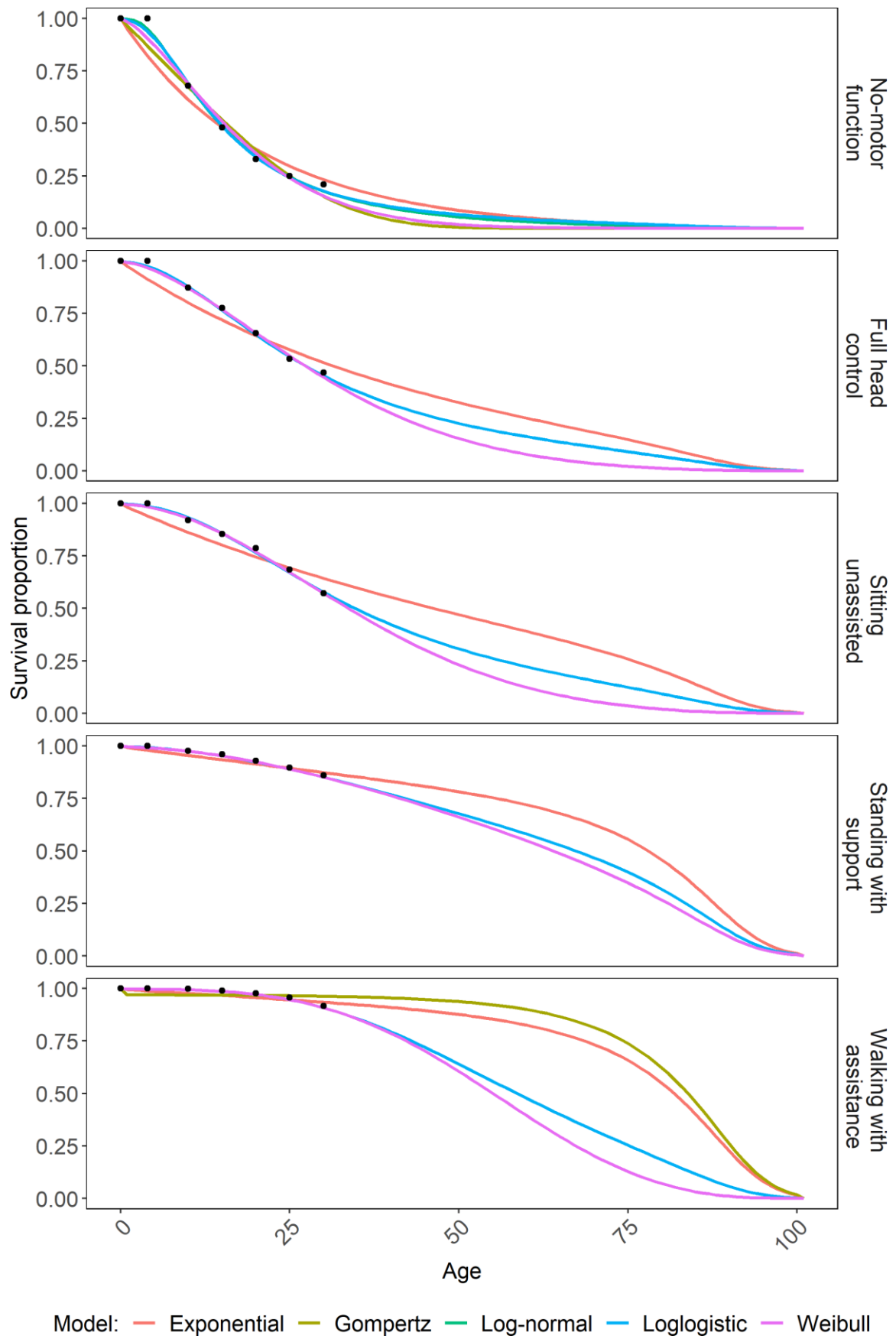


Figure S3. Results of the models for the survival extrapolations based on estimates from Brooks et al. (2014) adjusted for background mortality (23)

*Table S4 Motor milestone state utility values (TTO and SG studies) (25)*

| <b>Motor milestone state</b> | <b>TTO utility values</b> | <b>SG utility values</b> |
|------------------------------|---------------------------|--------------------------|
| No-motor function            | 0.494                     | 0.563                    |
| Full-head alignment          | 0.537                     | 0.573                    |
| Sitting (unaided)            | 0.631                     | 0.671                    |
| Standing with support        | 0.676                     | 0.710                    |
| Walking with assistance      | 0.728                     | 0.749                    |

Key: TTO, Time Trade Off; SG, Standard Gamble

*Table S5 Caregiver disutility values and number of caregivers*

| <b>Motor milestone state</b> | <b>Acaster et al. (2013)(29)</b> | <b>Gani et al. (2008) (30)</b> | <b>Number of caregivers</b> |
|------------------------------|----------------------------------|--------------------------------|-----------------------------|
| No-motor function            | 0.09                             | 0.11                           | 2.2                         |
| Full-head alignment          | 0.09                             | 0.11                           | 1.9                         |
| Sitting (unaided)            | 0.03                             | 0.05                           | 1.6                         |
| Standing with support        | 0.03                             | 0.05                           | 1.3                         |
| Walking with assistance      | 0.00                             | 0.00                           | 1.2                         |

Table S6 Annual number of follow-up visits, hospitalisation, and A&E attendance (per patient) (32)

| Resource use         | No-motor function | Full-head control | Sitting unassisted | Standing with support | Walking with assistance |
|----------------------|-------------------|-------------------|--------------------|-----------------------|-------------------------|
| Dietician            | 1.00              | 1.00              | 0.73               | 0.45                  | 0.45                    |
| Endocrinologist      | 0.00              | 0.00              | 0.00               | 0.00                  | 0.00                    |
| Gastroenterologist   | 1.88              | 1.88              | 1.09               | 0.30                  | 0.30                    |
| General practitioner | 2.13              | 2.13              | 1.79               | 1.45                  | 1.45                    |
| Geneticist           | 0.00              | 0.00              | 0.00               | 0.00                  | 0.00                    |
| Neurologist          | 2.50              | 2.50              | 2.08               | 1.65                  | 1.65                    |
| Nurse                | 0.00              | 0.00              | 0.15               | 0.30                  | 0.30                    |
| Occupational therapy | 39.25             | 39.25             | 22.23              | 5.20                  | 5.20                    |
| Ophthalmologist      | 0.75              | 0.75              | 0.43               | 0.10                  | 0.10                    |
| Orthopaedic surgeon  | 0.13              | 0.13              | 0.16               | 0.20                  | 0.20                    |
| Otolaryngologist     | 0.00              | 0.00              | 0.05               | 0.10                  | 0.10                    |
| Paediatrician        | 1.50              | 1.50              | 1.55               | 1.60                  | 1.60                    |
| Physiotherapist      | 84.80             | 84.80             | 55.72              | 26.65                 | 26.65                   |
| Pulmonologists       | 0.00              | 0.00              | 0.00               | 0.00                  | 0.00                    |
| Psychiatrist         | 0.50              | 0.50              | 3.33               | 6.15                  | 6.15                    |
| Psychologist         | 0.00              | 0.00              | 0.00               | 0.00                  | 0.00                    |
| Speech therapist     | 16.31             | 16.31             | 26.35              | 36.40                 | 36.40                   |
| Hospitalisation      | 1.88              | 1.88              | 1.39               | 0.90                  | 0.90                    |
| A&E attendance       | 1.25              | 1.25              | 0.63               | 0.00                  | 0.00                    |

Key: A&E, Accident and Emergency;

Table S7 Unit costs for specialist visits, hospitalisations, and A&E attendances

| Resource use         | Cost      | Source                                                                                                                                    |
|----------------------|-----------|-------------------------------------------------------------------------------------------------------------------------------------------|
| Dietician            | £62.00    | PSSRU 2021: Band 7 Dietitian cost per hour (page 150) (34)                                                                                |
| Endocrinologist      | £293.42   | National Schedule of Reference Costs 2020/2021: paediatric endocrinology, non-admitted F2F follow-up visit (WF01A) (33)                   |
| Gastroenterologist   | £261.96   | National Schedule of Reference Costs 2020/2021: paediatric gastroenterologist, non-admitted F2F follow-up visit (WF01A) (33)              |
| General practitioner | £39.23    | PSSRU 2021: cost of GP consultation lasting 9.22 minutes (with qualification including direct care staff costs) (34)                      |
| Geneticist           | £481.94   | National Schedule of Reference Costs 2020/2021: clinical genetics, non-admitted F2F follow-up visit (WF01A) (33)                          |
| Neurologist          | £371.19   | National Schedule of Reference Costs 2020/2021: paediatric neuro-disabilities, non-admitted F2F follow-up visit (WF01A) (33)              |
| Nurse                | £10.50    | PSSRU 2021: cost of nurse (at GP practice) lasting 15 minutes (34)                                                                        |
| Occupational therapy | £160.00   | PSSRU 2021: Occupational therapy services for children's health (page 70) (34)                                                            |
| Ophthalmologist      | £148.08   | National Schedule of Reference Costs 2020/2021: paediatric ENT, non-admitted F2F follow-up visit (WF01A) (33)                             |
| Orthopaedic surgeon  | £200.75   | National Schedule of Reference Costs 2020/2021: paediatric trauma and orthopaedics, non-admitted F2F follow-up visit (WF01A) (33)         |
| Otolaryngologist     | £148.08   | National Schedule of Reference Costs 2020/2021: paediatric ENT, non-admitted F2F follow-up visit (WF01A) (33)                             |
| Paediatrician        | £307.92   | National Schedule of Reference Costs 2020/2021: paediatrics, non-admitted F2F follow-up visit (WF01A) (33)                                |
| Physiotherapist      | £63.00    | National Schedule of Reference Costs 2020/2021: physiotherapy, non-admitted F2F follow-up visit (WF01A) (33)                              |
| Pulmonologists       | £305.19   | National Schedule of Reference Costs 2020/2021: respiratory medicine, non-admitted F2F follow-up visit (WF01A) (33)                       |
| Psychiatrist         | £378.06   | National Schedule of Reference Costs 2020/2021: child and adolescent psychiatry, non-admitted F2F follow-up visit (WF01A) (33)            |
| Psychologist         | £88.34    | National Schedule of Reference Costs 2019/2020: psychotherapy, non-admitted F2F follow-up visit (WF01A) (33)                              |
| Speech therapist     | £62.00    | PSSRU 2021: Band 7 Speech therapist cost per hour (page 150) (34)                                                                         |
| Hospitalisation      | £2,964.46 | National Schedule of Reference Costs 2020/2021: elective inpatient for special screening, examinations and genetic disorders (WH15Z) (33) |
| A&E attendance       | £332.46   | National Schedule of reference costs 2020/2021: weighted average of A&E admission and emergency medicine (VB01Z-VB09Z) (33)               |

Key: A&E, Accident and Emergency; ENT, ear/nose/throat; F2F, face-to-face

Table S8 Annual resource usage for medical procedures (per patient)

| Medical procedure               | No-motor function | Full-head control | Sitting unassisted | Standing with support | Walking with assistance |
|---------------------------------|-------------------|-------------------|--------------------|-----------------------|-------------------------|
| Barium swallow test             | 0.19              | 0.19              | 0.09               | 0.00                  | 0.00                    |
| Blood test                      | 0.88              | 0.88              | 0.87               | 1.00                  | 1.00                    |
| Coagulation test (PT, INR, PTT) | 0.75              | 0.75              | 0.73               | 0.90                  | 0.90                    |
| Electroencephalography          | 0.75              | 0.75              | 0.45               | 0.10                  | 0.10                    |
| Folic acid dosage in CSF        | 0.00              | 0.00              | 0.03               | 0.03                  | 0.03                    |
| Glycemia NT dosage in CSF       | 0.13              | 0.13              | 0.06               | 0.00                  | 0.00                    |
| Iron dosage                     | 0.88              | 0.88              | 0.87               | 1.00                  | 1.00                    |
| Lumbar puncture                 | 0.03              | 0.03              | 0.04               | 0.03                  | 0.03                    |
| MRI (cerebral)                  | 0.35              | 0.35              | 0.26               | 0.15                  | 0.15                    |
| ECG                             | 0.75              | 0.75              | 0.88               | 1.30                  | 1.30                    |
| Non-Bruininks-Oseretsky test    | 0.00              | 0.00              | 0.00               | 0.00                  | 0.00                    |
| Plasma AADC dosage              | 0.00              | 0.00              | 0.00               | 0.03                  | 0.03                    |
| Prolactin dosage                | 1.00              | 1.00              | 0.97               | 1.15                  | 1.15                    |
| Urine test                      | 0.75              | 0.75              | 0.81               | 1.00                  | 1.00                    |
| Urine vanillic acid level       | 0.13              | 0.13              | 0.06               | 0.00                  | 0.00                    |
| X-ray (hip)                     | 0.25              | 0.25              | 0.13               | 0.00                  | 0.00                    |
| X-ray (pelvis)                  | 0.25              | 0.25              | 0.13               | 0.00                  | 0.00                    |
| X-ray (spine)                   | 0.25              | 0.25              | 0.23               | 0.15                  | 0.15                    |

Key: MRI, magnetic resonance imaging

Table S9 Unit costs for medical and technical procedures

| Specialist                      | Cost      | Source                                                                                                                                              |
|---------------------------------|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------|
| Barium swallow test             | £179.58   | National Schedule of Reference Costs 2020/2021: weighted average of CT scan of one area, without contrast, 18 years and under (RD20B - RD20C) (33)  |
| Blood test                      | £3.63     | National Schedule of Reference Costs 2020/2021 - DAPS05 (33)                                                                                        |
| Coagulation test (PT, INR, PTT) | £3.63     | National Schedule of Reference Costs 2020/2021 - DAPS05 (33)                                                                                        |
| Electroencephalography          | £443      | National Schedule of Reference Costs 2020/2021: conventional EEG, EMG or Nerve Conduction Studies, 18 years and under (AA33D) (33)                  |
| Folic acid dosage in CSF        | £3.63     | Assumed equal to blood test                                                                                                                         |
| Glycemia NT dosage in CSF       | £3.63     | Assumed equal to blood test                                                                                                                         |
| Iron dosage                     | £3.63     | Assumed equal to blood test                                                                                                                         |
| Lumbar puncture                 | £1,846.82 | National Schedule of Reference Costs 2020/2021: weighted average of day case cost for diagnostic spinal puncture (HC72B and HC72C) (33)             |
| MRI (cerebral)                  | £268.65   | National Schedule of Reference Costs 2020/2021: weighted average of MRI scan of one area, without contrast, 18 years and under (RD01B - RD01C) (33) |
| ECG                             | £190.87   | National Schedule of Reference Costs 2020/2021: Electrocardiogram Monitoring or Stress Testing (EY51Z) (33)                                         |
| Non-Bruininks-Oseretsky test    | £160.00   | Assumed equal to occupational therapy appointment                                                                                                   |

| Specialist                   | Cost      | Source                                                                                                                                             |
|------------------------------|-----------|----------------------------------------------------------------------------------------------------------------------------------------------------|
| Plasma AADC dosage           | £57.07    | National Schedule of Reference Costs 2020/2021: special Screening, Examinations or Other Genetic Disorders (WH15Z) (33)                            |
| Prolactin dosage             | £3.63     | Assumed equal to blood test                                                                                                                        |
| Urine test                   | £1.85     | Assumed equal to Urine vanillactic test                                                                                                            |
| Urine vanillactic acid level | £1.85     | National Schedule of Reference Costs 2020/2021 - DAPS04 (33)                                                                                       |
| X-ray (hip)                  | £179.58   | National Schedule of Reference Costs 2020/2021: weighted average of CT scan of one area, without contrast, 18 years and under (RD20B - RD20C) (33) |
| X-ray (pelvis)               | £179.58   | National Schedule of Reference Costs 2020/2021: weighted average of CT scan of one area, without contrast, 18 years and under (RD20B - RD20C) (33) |
| X-ray (spine)                | £179.58   | National Schedule of Reference Costs 2020/2021: weighted average of CT scan of one area, without contrast, 18 years and under (RD20B - RD20C) (33) |
| Upper limb splints           | £123.70   | Clinician input                                                                                                                                    |
| Lower limb splints           | £360.78   | Clinician input                                                                                                                                    |
| Manual wheelchair            | £103.00   | PSSRU 2021: Self or attendant propelled chair (page 88) (Annual cost + maintenance)(34)                                                            |
| Electric wheelchair          | £481.00   | PSSRU 2021: Powered chair (page 88) (Annual cost + maintenance) (34)                                                                               |
| Verticalizers                | £2,750.79 | Goodwin et al. 2017, inflated to 2019/2020 year using PSSRU 2020 inflation indices                                                                 |

Abbreviations: CT, computed tomography; EEG; electroencephalography; MRI, magnetic resonance imaging

*Table S10 Treatment-emergent adverse events costs (per patient)*

| Treatment-emergent adverse events | Cost for moderate event | Cost for severe event | Source                                                                                                                                                                                                                                                                                                                                        |
|-----------------------------------|-------------------------|-----------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Dyskinesia                        | £3,362.02               | £7,680.34             | National Schedule of Reference Costs 2020/2021 cost for Paediatric Nervous System Disorders, weighted by day case / non-elective short stay by the proportion requiring hospitalisation for moderate and severe dyskinesia (PR01A:E) (33)<br>Moderate: 55% of cases require hospitalisation.<br>Severe: 100% of cases require hospitalisation |
| Pneumonia                         | £1,916.25               | £3,013.36             | National Schedule of Reference Costs 2020/2021: cost for pneumonia (DZ11R and DZ11S for severe and DZ11T and DZ11U for moderate) (33)<br>Moderate: Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 4-9<br>Severe: Lobar, Atypical or Viral Pneumonia, without Interventions, with CC Score 10+                       |
| Gastroenteritis                   | £823.54                 | £752.23               | National Schedule of Reference Costs 2020/2021: day case cost for paediatric gastroenteritis (PF21A and PF21B) (33)<br>Moderate: Paediatric, Infectious or Non-Infectious Gastroenteritis, with CC Score 0<br>Severe: Paediatric, Infectious or Non-Infectious Gastroenteritis, with CC Score 1+                                              |
| Gastrointestinal disorders        | £948.27                 | £833.50               | Moderate: National Schedule of Reference Costs 2020/21: day case cost for paediatric                                                                                                                                                                                                                                                          |

|  |  |  |                                                                               |
|--|--|--|-------------------------------------------------------------------------------|
|  |  |  | gastroenteritis (PF26A and PF26B for severe and PF26C and PF26D for moderate) |
|--|--|--|-------------------------------------------------------------------------------|

Table S11. Scenario analyses

| Model setting                                  | Base case                        | Scenario                                                                                                                                                                       |
|------------------------------------------------|----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Discount rates for costs and effects           | 1.5% for cost and effects        | 3.5% for costs and effects<br>0% for costs and effects                                                                                                                         |
| Time horizon                                   | Lifetime                         | 5 years<br>10 years<br>20 years                                                                                                                                                |
| Model specification                            | Asymptotic (30 patients)         | Gompertz (30 patients)<br>Gompertz (22 patients)<br>Asymptotic (22 patients)                                                                                                   |
| Length of developmental phase                  | 12 years                         | 5 years<br>10 years                                                                                                                                                            |
| Improvement in motor milestone achievement BSC | Yes – Natural history database   | Yes – 2% per year<br>No                                                                                                                                                        |
| Source for survival                            | Brooks et al. (2014) (23)        | Brooks et al. (2014) using exponential distribution for all health states<br>Brooks et al. (2014) using Weibull distribution for all health states<br>Blair et al. (2019) (37) |
| Source of utility                              | UK TTO study (25)                | UK SG study (25)                                                                                                                                                               |
| Bereavement disutility                         | Yes (38)                         | No                                                                                                                                                                             |
| Caregiver disutility                           | Yes – Acaster et al. (2013) (29) | No<br>Yes – Gani et al. (2008) (30)                                                                                                                                            |

\* This value is chosen based on the clinical trials showing that more than half of patients have reached their plateau in the PDMS-2 at 5 years.

Key: BSC, best supportive care; QoL, quality of life; SG, standard gamble; TTO, time trade-off

Table S12 Results: scenario analyses

| Scenario                                                                 | Incremental QALYs |
|--------------------------------------------------------------------------|-------------------|
| Base case                                                                | 12.182            |
| Discount rate – 3.5% p.a.                                                | 7.192             |
| Discount rate - 0% p.a.                                                  | 20.215            |
| Time horizon: 5 years                                                    | 0.857             |
| Time horizon: 10 years                                                   | 2.043             |
| Time horizon: 20 years                                                   | 4.454             |
| Model specification: (n=22) Asymptotic                                   | 14.498            |
| Model specification: (n=22) Gompertz                                     | 13.372            |
| Model specification: (n=30) Gompertz                                     | 11.546            |
| Modelling motor milestones through observed distribution                 | 10.824            |
| Length of developmental phase: 5 years                                   | 11.831            |
| Length of developmental phase: 10 years                                  | 12.171            |
| Improvement in motor milestone achievement for BSC patients: 2% per year | 12.038            |
| No improvement in motor milestone achievement for BSC patients           | 12.931            |

|                                                               |        |
|---------------------------------------------------------------|--------|
| Expected survival Brooks et al. (2014) (23): CP (Exponential) | 12.972 |
| Expected survival Brooks et al. (2014) (23): CP (Weibull)     | 10.868 |
| Proxy survival from CP: Blair et al. (2019) (37)              | 11.221 |
| Source of utility: SG study (UK) (29)                         | 12.251 |
| No caregiver disutility                                       | 11.191 |
| Source of caregiver disutility: Gani et al. (2008) (30)       | 12.145 |