



Clinical trial results:

Efficacy assessment of systematic folinic acid and thyroid hormone treatment on the psychomotor development of young Down Syndrome children. ACTHYF

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2010-021134-66 |
| Trial protocol | FR |
| Global end of trial date | 31 May 2018 |

Results information

| | |
|-----------------------------------|---|
| Result version number | v1 (current) |
| This version publication date | 01 January 2020 |
| First version publication date | 01 January 2020 |
| Summary attachment (see zip file) | CSR Synopsis (_CSR_ACTHYF_Final v1.0_11Dec18_Summary.pdf) |

Trial information

Trial identification

| | |
|-----------------------|---------------|
| Sponsor protocol code | IJL-AFHT-TH10 |
|-----------------------|---------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01576705 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Institut Jérôme Lejeune |
| Sponsor organisation address | 37 rue des Volontaires, Paris, France, 75015 |
| Public contact | Dr Clotilde Mircher, Institut Jérôme Lejeune, 33 156586300, clotildemircher@institutlejeune.org |
| Scientific contact | Dr Clotilde Mircher, Institut Jérôme Lejeune, 33 156586300, clotilde.mircher@institutlejeune.org |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|--------------|
| Analysis stage | Final |
| Date of interim/final analysis | 25 June 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 31 May 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 31 May 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Evaluation of the following in new born infants and very young children with Down syndrome:

- the efficacy of systematic treatment with L-thyroxin at controlled doses (clinically and by ultrasensitive TSH)
- the efficacy of systematic folinic acid treatment at a dose of 1 mg/kg/d
- any interaction between these two treatments

Protection of trial subjects:

Patients must be available 4 hours, spread over half a day, or before and after the meal, so that they can have a period of rest between the medical consultation and the psychological evaluation.

For each blood test performed, a patch of EMLA cream was proposed to avoid the pain related to the levy.

Background therapy:

During the study, the Investigator or the patient's routine treating physician could prescribe concomitant medications or supportive therapy deemed necessary

Evidence for comparator:

Placebo control was used in the absence of a standard of care

| | |
|---|---------------|
| Actual start date of recruitment | 02 April 2012 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | France: 175 |
| Worldwide total number of subjects | 175 |
| EEA total number of subjects | 175 |

Notes:

Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |

| | |
|--|-----|
| Infants and toddlers (28 days-23 months) | 175 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Recruitment date : April 2nd 2012 - December 15th 2016

Centre : Institut Jérôme Lejeune, Paris -France

Pre-assignment

Screening details:

685 patients assessed for eligibility :

- 82 refused participation
- 196 lost to follow-up after initial contact
- 232 ineligible (mostly hypothyroidism, prematurity)
- 175 patients included and randomized

Period 1

| | |
|------------------------------|---------------------------------|
| Period 1 title | over all trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo |

Arm description:

double placebo: Thyroxin placebo+ folinic acid placebo

| | |
|--|---|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo L-thyroxin tablets (D2M) + Placebo folinic acid capsules (Therabel) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo L-thyroxin tablets (D2M): identical excipients and presentation as active product

Placebo folinic acid capsules (Therabel): identical excipients and presentation as active product

| | |
|------------------|------------------|
| Arm title | Folinic acid: FA |
|------------------|------------------|

Arm description:

folinic acid + L-thyroxin placebo

| | |
|--|----------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Folinic acid |
| Investigational medicinal product code | |
| Other name | Folinoral®, Therabel |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Folinic acid (Folinoral®, Therabel): 5 mg capsules, 1.0 ± 0.3 mg/kg/d, oral; commercial preparation

| | |
|------------------|------------|
| Arm title | L-thyroxin |
|------------------|------------|

Arm description:

L-thyroxin+ folinic acid placebo

| | |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

| | |
|--|--------------------|
| Investigational medicinal product name | L-thyroxin |
| Investigational medicinal product code | |
| Other name | Lévothyrox®, Merck |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

L-thyroxin (Lévothyrox®, Merck): 25 µg tablets, controlled dose initiated at 3.0 ± 0.2 µg/kg/d, oral; commercial preparation

| | |
|------------------|-----------------|
| Arm title | FA + L-thyroxin |
|------------------|-----------------|

Arm description:

Folinic acid + L-thyroxin

| | |
|--|--|
| Arm type | Active comparator |
| Investigational medicinal product name | folinic acid + L-thyroxin |
| Investigational medicinal product code | |
| Other name | Folinoral®, Therabel+ Lévothyrox®, Merck |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

L-thyroxin (Lévothyrox®, Merck): 25 µg tablets, controlled dose initiated at 3.0 ± 0.2 µg/kg/d, oral; commercial preparation

Folinic acid (Folinoral®, Therabel): 5 mg capsules, 1.0 ± 0.3 mg/kg/d, oral; commercial preparation

| Number of subjects in period 1^[1] | Placebo | Folinic acid: FA | L-thyroxin |
|---|---------|------------------|------------|
| Started | 41 | 38 | 37 |
| Analyzed | 41 | 38 | 37 |
| Completed | 37 | 30 | 34 |
| Not completed | 4 | 8 | 3 |
| Adverse event, serious fatal | - | - | - |
| Physician decision | 1 | 1 | 1 |
| Consent withdrawn by subject | - | - | 1 |
| Adverse event, non-fatal | - | 7 | 1 |
| Protocol deviation | 3 | - | - |

| Number of subjects in period 1^[1] | FA + L-thyroxin |
|---|-----------------|
| Started | 40 |
| Analyzed | 40 |
| Completed | 37 |
| Not completed | 3 |
| Adverse event, serious fatal | 1 |
| Physician decision | - |
| Consent withdrawn by subject | - |
| Adverse event, non-fatal | - |

| | |
|--------------------|---|
| Protocol deviation | 2 |
|--------------------|---|

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 175 is the number of randomised patients

156 is the number of The modified ITT (mITT) population excluded the 18 patients who discontinued prematurely due to presence of elevated TSH levels at baseline , as well as the patient lacking a complete informed consent, and was thus composed of 156 patients. The main analysis of the primary endpoint was performed in the mITT.

Safety was analysed in the safety population. The safety population excluded the untreated patient (randomised to L-thyroxin).

Baseline characteristics

Reporting groups

| | |
|--|------------------|
| Reporting group title | Placebo |
| Reporting group description: double placebo: Thyroxin placebo+ folinic acid placebo | |
| Reporting group title | Folinic acid: FA |
| Reporting group description: folinic acid + L-thyroxin placebo | |
| Reporting group title | L-thyroxin |
| Reporting group description: L-thyroxin+ folinic acid placebo | |
| Reporting group title | FA + L-thyroxin |
| Reporting group description: Folinic acid + L-thyroxin | |

| Reporting group values | Placebo | Folinic acid: FA | L-thyroxin |
|---|---------|------------------|------------|
| Number of subjects | 41 | 38 | 37 |
| Age categorical | | | |
| Units: Subjects | | | |
| 6-12 Months | 20 | 20 | 19 |
| 12-18 Months | 21 | 18 | 18 |
| Age continuous | | | |
| Almost all baseline characteristics were very well balanced between groups in the mITT population; median age was ~12 months in all groups. | | | |
| Units: months | | | |
| arithmetic mean | 12.7 | 12.3 | 12.2 |
| standard deviation | ± 3.3 | ± 4.0 | ± 3.8 |
| Gender categorical | | | |
| There were 55.3% to 58.5% males across groups. | | | |
| Units: Subjects | | | |
| Female | 17 | 17 | 16 |
| Male | 24 | 21 | 21 |
| karyotype | | | |
| Patient with a karyotype demonstrating homogeneous, free and complete or Robertsonian translocation trisomy 21 are included. All but 2 mITT patients (98.7%) had a free karyotype. | | | |
| Units: Subjects | | | |
| karyotype free and complete | 40 | 38 | 37 |
| Karyotype Robertsonian translocation | 1 | 0 | 0 |
| cardiac abnormalities | | | |
| Isolated heart murmur yes for subjects with isolated heart murmur | | | |
| Isolated heart murmur no for subjects without isolated heart murmur | | | |
| Units: Subjects | | | |
| Isolated heart murmur yes | 1 | 2 | 3 |
| Isolated heart murmur no | 40 | 36 | 34 |
| cardiac abnormalities | | | |
| Atrioventricular septal defect (AVSD) YES for subjects with Atrioventricular septal defect | | | |

| | | | |
|---|--------|--------|--------|
| Atrioventricular septal defect (AVSD) NO for subjects without Atrioventricular septal defect | | | |
| Units: Subjects | | | |
| Atrioventricular septal defect (AVSD) YES | 2 | 1 | 1 |
| Atrioventricular septal defect (AVSD) NO | 39 | 37 | 35 |
| Not recorded | 0 | 0 | 1 |
| cardiac abnormalities | | | |
| Ventricular septal defect YES for subjects with Ventricular septal defect | | | |
| Ventricular septal defect NO for subjects without Ventricular septal defect | | | |
| Units: Subjects | | | |
| Ventricular septal defect YES | 10 | 7 | 5 |
| Ventricular septal defect NO | 31 | 31 | 31 |
| Not recorded | 0 | 0 | 1 |
| cardiac abnormalities | | | |
| Atrial septal defect YES for subjects with Atrial septal defect | | | |
| Atrial septal defect No for subjects without Atrial septal defect | | | |
| Units: Subjects | | | |
| Atrial septal defect YES | 10 | 8 | 11 |
| Atrial septal defect No | 31 | 30 | 26 |
| cardiac abnormalities | | | |
| Patient ductus arteriosus YES for subjects with ductus arteriosus | | | |
| Patient ductus arteriosus NO for subjects without ductus arteriosus | | | |
| Units: Subjects | | | |
| Patient ductus arteriosus YES | 6 | 7 | 6 |
| Patient ductus arteriosus NO | 35 | 31 | 30 |
| Not recorded | 0 | 0 | 1 |
| cardiac abnormalities | | | |
| Mitral valve prolapse (except AVSD) YES for subjects with Mitral valve prolapse (except AVSD) | | | |
| Mitral valve prolapse (except AVSD) NO for subjects without Mitral valve prolapse (except AVSD) | | | |
| Units: Subjects | | | |
| Mitral valve prolapse (except AVSD) YES | 0 | 0 | 0 |
| Mitral valve prolapse (except AVSD) NO | 41 | 38 | 36 |
| Not recorded | 0 | 0 | 1 |
| cardiac abnormalities | | | |
| Other cardiac abnormalities YES for subjects with Other cardiac abnormalities | | | |
| Other cardiac abnormalities NO for subjects without Other cardiac abnormalities | | | |
| Units: Subjects | | | |
| Other cardiac abnormalities YES | 9 | 7 | 7 |
| Other cardiac abnormalities NO | 32 | 31 | 29 |
| Not recorded | 0 | 0 | 1 |
| height | | | |
| Patients had a mean height of ~71 cm | | | |
| Units: cm | | | |
| arithmetic mean | 71.68 | 71.13 | 71.14 |
| standard deviation | ± 4.36 | ± 4.15 | ± 5.03 |
| pregnancy duration | | | |

| | | | |
|---|--------|--------|--------|
| patients with gestational age < 231 days (35 weeks of amenorrhoea = 33 weeks of gestation) are excluded | | | |
| Units: weeks of amenorrhoea | | | |
| arithmetic mean | 37.85 | 38.29 | 38.14 |
| standard deviation | ± 0.99 | ± 1.33 | ± 0.98 |
| TSH | | | |
| Exclusion criteria: Patient with hypothyroidism demonstrated by laboratory tests with TSH >7 mIU/L | | | |
| Units: mIU/L | | | |
| arithmetic mean | 4.45 | 4.79 | 4.32 |
| standard deviation | ± 1.49 | ± 1.23 | ± 1.52 |
| weight | | | |
| Units: kg | | | |
| arithmetic mean | 8.62 | 8.52 | 8.19 |
| standard deviation | ± 1.6 | ± 1.13 | ± 1.42 |

| | | | |
|---|-----------------|-------|--|
| Reporting group values | FA + L-thyroxin | Total | |
| Number of subjects | 40 | 156 | |
| Age categorical | | | |
| Units: Subjects | | | |
| 6-12 Months | 21 | 80 | |
| 12-18 Months | 19 | 76 | |
| Age continuous | | | |
| Almost all baseline characteristics were very well balanced between groups in the mITT population; median age was ~12 months in all groups. | | | |
| Units: months | | | |
| arithmetic mean | 12.3 | | |
| standard deviation | ± 3.4 | - | |
| Gender categorical | | | |
| There were 55.3% to 58.5% males across groups. | | | |
| Units: Subjects | | | |
| Female | 17 | 67 | |
| Male | 23 | 89 | |
| karyotype | | | |
| Patient with a karyotype demonstrating homogeneous, free and complete or Robertsonian translocation trisomy 21 are included. All but 2 mITT patients (98.7%) had a free karyotype. | | | |
| Units: Subjects | | | |
| karyotype free and complete | 39 | 154 | |
| Karyotype Robertsonian translocation | 1 | 2 | |
| cardiac abnormalities | | | |
| Isolated heart murmur yes for subjects with isolated heart murmur | | | |
| Isolated heart murmur no for subjects without isolated heart murmur | | | |
| Units: Subjects | | | |
| Isolated heart murmur yes | 1 | 7 | |
| Isolated heart murmur no | 39 | 149 | |
| cardiac abnormalities | | | |
| Atrioventricular septal defect (AVSD) YES for subjects with Atrioventricular septal defect | | | |
| Atrioventricular septal defect (AVSD) NO for subjects without Atrioventricular septal defect | | | |
| Units: Subjects | | | |
| Atrioventricular septal defect (AVSD) YES | 2 | 6 | |

| | | | |
|---|--------|-----|--|
| Atrioventricular septal defect (AVSD) NO | 38 | 149 | |
| Not recorded | 0 | 1 | |
| cardiac abnormalities | | | |
| Ventricular septal defect YES for subjects with Ventricular septal defect | | | |
| Ventricular septal defect NO for subjects without Ventricular septal defect | | | |
| Units: Subjects | | | |
| Ventricular septal defect YES | 5 | 27 | |
| Ventricular septal defect NO | 35 | 128 | |
| Not recorded | 0 | 1 | |
| cardiac abnormalities | | | |
| Atrial septal defect YES for subjects with Atrial septal defect | | | |
| Atrial septal defect No for subjects without Atrial septal defect | | | |
| Units: Subjects | | | |
| Atrial septal defect YES | 15 | 44 | |
| Atrial septal defect No | 25 | 112 | |
| cardiac abnormalities | | | |
| Patient ductus arteriosus YES for subjects with ductus arteriosus | | | |
| Patient ductus arteriosus NO for subjects without ductus arteriosus | | | |
| Units: Subjects | | | |
| Patient ductus arteriosus YES | 6 | 25 | |
| Patient ductus arteriosus NO | 34 | 130 | |
| Not recorded | 0 | 1 | |
| cardiac abnormalities | | | |
| Mitral valve prolaspse (except AVSD) YES for subjects with Mitral valve prolaspse (except AVSD) | | | |
| Mitral valve prolaspse (except AVSD) NO for subjects without Mitral valve prolaspse (except AVSD) | | | |
| Units: Subjects | | | |
| Mitral valve prolaspse (except AVSD) YES | 0 | 0 | |
| Mitral valve prolaspse (except AVSD) NO | 40 | 155 | |
| Not recorded | 0 | 1 | |
| cardiac abnormalities | | | |
| Other cardiac abnormalities YES for subjects with Other cardiac abnormalities | | | |
| Other cardiac abnormalities NO for subjects without Other cardiac abnormalities | | | |
| Units: Subjects | | | |
| Other cardiac abnormalities YES | 9 | 32 | |
| Other cardiac abnormalities NO | 31 | 123 | |
| Not recorded | 0 | 1 | |
| height | | | |
| Patients had a mean height of ~71 cm | | | |
| Units: cm | | | |
| arithmetic mean | 70.86 | | |
| standard deviation | ± 3.88 | - | |
| pregnancy duration | | | |
| patients with gestational age < 231 days (35 weeks of amenorrhoea = 33 weeks of gestation) are excluded | | | |
| Units: weeks of amenorrhoea | | | |
| arithmetic mean | 38.03 | | |
| standard deviation | ± 1.37 | - | |

| | | | |
|--|-------|---|--|
| TSH | | | |
| Exclusion criteria: Patient with hypothyroidism demonstrated by laboratory tests with TSH >7 mIU/L | | | |
| Units: mIU/L | | | |
| arithmetic mean | 4.3 | | |
| standard deviation | ± 1.7 | - | |
| weight | | | |
| Units: kg | | | |
| arithmetic mean | 8.3 | | |
| standard deviation | ± 1.2 | - | |

Subject analysis sets

| | |
|--|-----------------------------|
| Subject analysis set title | mITT |
| Subject analysis set type | Modified intention-to-treat |
| Subject analysis set description: | |
| All ITT patients who did not prematurely discontinue the study due to high baseline TSH levels (per exclusion criterion #8). | |
| Subject analysis set title | PP |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| All mITT patients having taken the study medication and without major protocol violations | |
| Subject analysis set title | ITT |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| All randomised patients with valid informed consent, regardless of whether they received study treatment | |
| Subject analysis set title | Safety |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: | |
| All randomised patients receiving at least one dose of study treatment | |
| Subject analysis set title | All-randomized |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| All randomised patients regardless of whether they received study treatment | |

| Reporting group values | mITT | PP | ITT |
|---|--------|-----|-----|
| Number of subjects | 156 | 138 | 175 |
| Age categorical | | | |
| Units: Subjects | | | |
| 6-12 Months | | | |
| 12-18 Months | | | |
| Age continuous | | | |
| Almost all baseline characteristics were very well balanced between groups in the mITT population; median age was ~12 months in all groups. | | | |
| Units: months | | | |
| arithmetic mean | 12.37 | | |
| standard deviation | ± 3.58 | ± | ± |
| Gender categorical | | | |
| There were 55.3% to 58.5% males across groups. | | | |
| Units: Subjects | | | |
| Female | 67 | | |
| Male | 89 | | |

| | | | |
|---|-----|--|--|
| karyotype | | | |
| Patient with a karyotype demonstrating homogeneous, free and complete or Robertsonian translocation trisomy 21 are included. All but 2 mITT patients (98.7%) had a free karyotype. | | | |
| Units: Subjects | | | |
| karyotype free and complete | 154 | | |
| Karyotype Robertsonian translocation | 2 | | |
| cardiac abnormalities | | | |
| Isolated heart murmur yes for subjects with isolated heart murmur | | | |
| Isolated heart murmur no for subjects without isolated heart murmur | | | |
| Units: Subjects | | | |
| Isolated heart murmur yes | | | |
| Isolated heart murmur no | | | |
| cardiac abnormalities | | | |
| Atrioventricular septal defect (AVSD) YES for subjects with Atrioventricular septal defect | | | |
| Atrioventricular septal defect (AVSD) NO for subjects without Atrioventricular septal defect | | | |
| Units: Subjects | | | |
| Atrioventricular septal defect (AVSD) YES | | | |
| Atrioventricular septal defect (AVSD) NO | | | |
| Not recorded | | | |
| cardiac abnormalities | | | |
| Ventricular septal defect YES for subjects with Ventricular septal defect | | | |
| Ventricular septal defect NO for subjects without Ventricular septal defect | | | |
| Units: Subjects | | | |
| Ventricular septal defect YES | | | |
| Ventricular septal defect NO | | | |
| Not recorded | | | |
| cardiac abnormalities | | | |
| Atrial septal defect YES for subjects with Atrial septal defect | | | |
| Atrial septal defect No for subjects without Atrial septal defect | | | |
| Units: Subjects | | | |
| Atrial septal defect YES | | | |
| Atrial septal defect No | | | |
| cardiac abnormalities | | | |
| Patient ductus arteriosus YES for subjects with ductus arteriosus | | | |
| Patient ductus arteriosus NO for subjects without ductus arteriosus | | | |
| Units: Subjects | | | |
| Patient ductus arteriosus YES | | | |
| Patient ductus arteriosus NO | | | |
| Not recorded | | | |
| cardiac abnormalities | | | |
| Mitral valve prolapse (except AVSD) YES for subjects with Mitral valve prolapse (except AVSD) | | | |
| Mitral valve prolapse (except AVSD) NO for subjects without Mitral valve prolapse (except AVSD) | | | |
| Units: Subjects | | | |
| Mitral valve prolapse (except AVSD) YES | | | |

| | | | |
|---|--------|---|---|
| Mitral valve prolapse (except AVSD) NO Not recorded | | | |
| cardiac abnormalities | | | |
| Other cardiac abnormalities YES for subjects with Other cardiac abnormalities | | | |
| Other cardiac abnormalities NO for subjects without Other cardiac abnormalities | | | |
| Units: Subjects | | | |
| Other cardiac abnormalities YES Other cardiac abnormalities NO Not recorded | | | |
| height | | | |
| Patients had a mean height of ~71 cm | | | |
| Units: cm | | | |
| arithmetic mean | 71.21 | | |
| standard deviation | ± 4.33 | ± | ± |
| pregnancy duration | | | |
| patients with gestational age < 231 days (35 weeks of amenorrhoea = 33 weeks of gestation) are excluded | | | |
| Units: weeks of amenorrhoea | | | |
| arithmetic mean | 38.07 | | |
| standard deviation | ± 1.18 | ± | ± |
| TSH | | | |
| Exclusion criteria: Patient with hypothyroidism demonstrated by laboratory tests with TSH >7 mIU/L | | | |
| Units: mIU/L | | | |
| arithmetic mean | 4.46 | | |
| standard deviation | ± 1.5 | ± | ± |
| weight | | | |
| Units: kg | | | |
| arithmetic mean | 8.42 | | |
| standard deviation | ± 1.35 | ± | ± |

| Reporting group values | Safety | All-randomized | |
|---|--------|----------------|--|
| Number of subjects | 174 | 175 | |
| Age categorical | | | |
| Units: Subjects | | | |
| 6-12 Months | | | |
| 12-18 Months | | | |
| Age continuous | | | |
| Almost all baseline characteristics were very well balanced between groups in the mITT population; median age was ~12 months in all groups. | | | |
| Units: months | | | |
| arithmetic mean | | | |
| standard deviation | ± | ± | |
| Gender categorical | | | |
| There were 55.3% to 58.5% males across groups. | | | |
| Units: Subjects | | | |
| Female | | | |
| Male | | | |
| karyotype | | | |
| Patient with a karyotype demonstrating homogeneous, free and complete or Robertsonian translocation trisomy 21 are included. All but 2 mITT patients (98.7%) had a free karyotype. | | | |

| | | | |
|---|--|--|--|
| Units: Subjects | | | |
| karyotype free and complete Karyotype Robertsonian translocation | | | |
| cardiac abnormalities | | | |
| Isolated heart murmur yes for subjects with isolated heart murmur | | | |
| Isolated heart murmur no for subjects without isolated heart murmur | | | |
| Units: Subjects | | | |
| Isolated heart murmur yes Isolated heart murmur no | | | |
| cardiac abnormalities | | | |
| Atrioventricular septal defect (AVSD) YES for subjects with Atrioventricular septal defect | | | |
| Atrioventricular septal defect (AVSD) NO for subjects without Atrioventricular septal defect | | | |
| Units: Subjects | | | |
| Atrioventricular septal defect (AVSD) YES Atrioventricular septal defect (AVSD) NO Not recorded | | | |
| cardiac abnormalities | | | |
| Ventricular septal defect YES for subjects with Ventricular septal defect | | | |
| Ventricular septal defect NO for subjects without Ventricular septal defect | | | |
| Units: Subjects | | | |
| Ventricular septal defect YES Ventricular septal defect NO Not recorded | | | |
| cardiac abnormalities | | | |
| Atrial septal defect YES for subjects with Atrial septal defect | | | |
| Atrial septal defect No for subjects without Atrial septal defect | | | |
| Units: Subjects | | | |
| Atrial septal defect YES Atrial septal defect No | | | |
| cardiac abnormalities | | | |
| Patient ductus arteriosus YES for subjects with ductus arteriosus | | | |
| Patient ductus arteriosus NO for subjects without ductus arteriosus | | | |
| Units: Subjects | | | |
| Patient ductus arteriosus YES Patient ductus arteriosus NO Not recorded | | | |
| cardiac abnormalities | | | |
| Mitral valve prolapse (except AVSD) YES for subjects with Mitral valve prolapse (except AVSD) | | | |
| Mitral valve prolapse (except AVSD) NO for subjects without Mitral valve prolapse (except AVSD) | | | |
| Units: Subjects | | | |
| Mitral valve prolapse (except AVSD) YES Mitral valve prolapse (except AVSD) NO Not recorded | | | |
| cardiac abnormalities | | | |
| Other cardiac abnormalities YES for subjects with Other cardiac abnormalities | | | |

| | | | |
|---|---|---|--|
| Other cardiac abnormalities NO for subjects without Other cardiac abnormalities | | | |
| Units: Subjects | | | |
| Other cardiac abnormalities YES | | | |
| Other cardiac abnormalities NO | | | |
| Not recorded | | | |
| height | | | |
| Patients had a mean height of ~71 cm | | | |
| Units: cm | | | |
| arithmetic mean | | | |
| standard deviation | ± | ± | |
| pregnancy duration | | | |
| patients with gestational age < 231 days (35 weeks of amenorrhoea = 33 weeks of gestation) are excluded | | | |
| Units: weeks of amenorrhoea | | | |
| arithmetic mean | | | |
| standard deviation | ± | ± | |
| TSH | | | |
| Exclusion criteria: Patient with hypothyroidism demonstrated by laboratory tests with TSH >7 mIU/L | | | |
| Units: mIU/L | | | |
| arithmetic mean | | | |
| standard deviation | ± | ± | |
| weight | | | |
| Units: kg | | | |
| arithmetic mean | | | |
| standard deviation | ± | ± | |

End points

End points reporting groups

| | |
|---|-----------------------------|
| Reporting group title | Placebo |
| Reporting group description: double placebo: Thyroxin placebo+ folic acid placebo | |
| Reporting group title | Folic acid: FA |
| Reporting group description: folic acid + L-thyroxin placebo | |
| Reporting group title | L-thyroxin |
| Reporting group description: L-thyroxin+ folic acid placebo | |
| Reporting group title | FA + L-thyroxin |
| Reporting group description: Folic acid + L-thyroxin | |
| Subject analysis set title | mITT |
| Subject analysis set type | Modified intention-to-treat |
| Subject analysis set description: All ITT patients who did not prematurely discontinue the study due to high baseline TSH levels (per exclusion criterion #8). | |
| Subject analysis set title | PP |
| Subject analysis set type | Per protocol |
| Subject analysis set description: All mITT patients having taken the study medication and without major protocol violations | |
| Subject analysis set title | ITT |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: All randomised patients with valid informed consent, regardless of whether they received study treatment | |
| Subject analysis set title | Safety |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: All randomised patients receiving at least one dose of study treatment | |
| Subject analysis set title | All-randomized |
| Subject analysis set type | Full analysis |
| Subject analysis set description: All randomised patients regardless of whether they received study treatment | |

Primary: Griffiths Mental Development Scales (GMDS)

| | |
|---|--|
| End point title | Griffiths Mental Development Scales (GMDS) |
| End point description: Adjusted change from baseline in Global Development Quotient (GDQ) at Visit 3 using the Griffiths Mental Development Scales (GMDS). | |
| End point type | Primary |
| End point timeframe: 12 months | |

| End point values | Placebo | Folinic acid: FA | L-thyroxin | FA + L-thyroxin |
|---|---------------------|---------------------|---------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 41 | 38 | 37 | 40 |
| Units: Adjusted change in GMDS GDQ value | | | | |
| arithmetic mean (confidence interval 95%) | -5.1 (-7.8 to -2.4) | -4.7 (-7.7 to -1.6) | -3.9 (-6.9 to -0.8) | -3.9 (-6.7 to -1.1) |

Statistical analyses

| Statistical analysis title | Comparison of treatment groups |
|---|---|
| Statistical analysis description: | |
| ANCOVA adjusted for covariates (sex, age class at randomisation, pair of neuropsychologists at Visit 1 and 3 and baseline value of GDQ) | |
| Comparison groups | Folinic acid: FA v L-thyroxin v FA + L-thyroxin v Placebo |
| Number of subjects included in analysis | 156 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | > 0.05 ^[1] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |

Notes:

[1] - Difference to placebo, unadjusted Student p-value:

- FA: p=0.3919

- L-Thyroxin: p=0.2019

-FA + L-Thyroxin: p=1878

Secondary: Brunet-Lézine psychomotor development scale (BL-R GDQ)

| End point title | Brunet-Lézine psychomotor development scale (BL-R GDQ) |
|---|--|
| End point description: | |
| Change from baseline in the Brunet-Lézine Revised (BL-R) GDQ at Visit 3 | |
| End point type | Secondary |
| End point timeframe: | |
| 12 months | |

| End point values | Placebo | Folinic acid: FA | L-thyroxin | FA + L-thyroxin |
|---|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 41 | 38 | 35 | 38 |
| Units: Brunet-Lézine Revised (BL-R) GDQ value | | | | |
| arithmetic mean (confidence interval 95%) | -8.9 (-11.7 to -6.1) | -8.3 (-11.4 to -5.2) | -8.0 (-11.1 to -4.9) | -8.7 (-11.5 to -5.8) |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | ANCOVA |
| Statistical analysis description: ANCOVA adjusted for covariates | |
| Comparison groups | Placebo v Folinic acid: FA v L-thyroxin v FA + L-thyroxin |
| Number of subjects included in analysis | 152 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | > 0.05 [2] |
| Method | ANCOVA |

Notes:

[2] - Difference to placebo: unadjusted Student p-value:

- FA: p=0.3575

- L-Thyroxin: p=0.2696

- FA+L-Thyroxin: p=0.4407

Secondary: Biometric parameters : Height

| | |
|--|-------------------------------|
| End point title | Biometric parameters : Height |
| End point description: Adjusted mean change from baseline in height | |
| End point type | Secondary |
| End point timeframe: 12 months | |

| End point values | Placebo | Folinic acid: FA | L-thyroxin | FA + L-thyroxin |
|---|-------------------|--------------------|------------------|-------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 41 | 38 | 37 | 40 |
| Units: cm | | | | |
| arithmetic mean (confidence interval 95%) | 9.9 (9.4 to 10.5) | 10.0 (9.3 to 10.7) | 9.3 (8.7 to 9.9) | 9.7 (9.2 to 10.3) |

Statistical analyses

No statistical analyses for this end point

Secondary: Biometric parameters: Head circumference

| | |
|--|--|
| End point title | Biometric parameters: Head circumference |
| End point description: Adjusted mean change from baseline in head circumference | |
| End point type | Secondary |
| End point timeframe: 12 months | |

| End point values | Placebo | Folinic acid: FA | L-thyroxin | FA + L-thyroxin |
|---|------------------|------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 41 | 38 | 37 | 40 |
| Units: cm | | | | |
| arithmetic mean (confidence interval 95%) | 2.0 (1.8 to 2.2) | 2.1 (1.9 to 2.3) | 2.1 (1.9 to 2.3) | 1.9 (1.7 to 2.1) |

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Exposure

| | |
|------------------------|-----------------|
| End point title | Safety Exposure |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 12 months | |

| End point values | Safety | | | |
|-----------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 174 | | | |
| Units: month | 11 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Adverse events (TEAE)

| | |
|--|------------------------------|
| End point title | Safety Adverse events (TEAE) |
| End point description: | |
| Almost all patients in the safety population experienced at least one TEAE (Treatment Emergent Adverse Event). | |
| End point type | Secondary |
| End point timeframe: | |
| 12 months | |

| End point values | Safety | | | |
|------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 174 | | | |
| Units: count of participants | 154 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Related TEAEs

| | |
|--|----------------------|
| End point title | Safety Related TEAEs |
| End point description: | |
| Related TEAEs (Treatment Emergent Adverse Event) | |
| End point type | Secondary |
| End point timeframe: | |
| 12 months | |

| End point values | Safety | | | |
|------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 174 | | | |
| Units: count of participants | 9 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Serious TEAEs

| | |
|---|----------------------|
| End point title | Safety Serious TEAEs |
| End point description: | |
| serious treatment emergent adverse events | |
| End point type | Secondary |
| End point timeframe: | |
| 12 months | |

| End point values | Safety | | | |
|------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 174 | | | |
| Units: count of participants | 30 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Safety TEAEs leading to treatment discontinuation

| | |
|---|---|
| End point title | Safety TEAEs leading to treatment discontinuation |
| End point description: | |
| adverse events leading to permanent discontinuation | |
| End point type | Secondary |
| End point timeframe: | |
| 12 months | |

| End point values | Safety | | | |
|------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 174 | | | |
| Units: count of participants | 7 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Safety Laboratory events

| | |
|---|--------------------------|
| End point title | Safety Laboratory events |
| End point description: | |
| Treatment emergent laboratory abnormalities | |
| End point type | Secondary |
| End point timeframe: | |
| 12 months | |

| | | | | |
|-----------------------------|----------------------|--|--|--|
| End point values | Safety | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 174 | | | |
| Units: participants count | 38 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Safety abnormal general examination

| | |
|-----------------|-------------------------------------|
| End point title | Safety abnormal general examination |
|-----------------|-------------------------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

12months

| | | | | |
|---|-----------------|------------------|-----------------|-----------------|
| End point values | Placebo | Folinic acid: FA | L-thyroxin | FA + L-thyroxin |
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 40 | 30 | 35 | 38 |
| Units: abnormal general examination count | 29 | 22 | 24 | 27 |

Statistical analyses

No statistical analyses for this end point

Secondary: Vital signs change from baseline : weight

| | |
|-----------------|---|
| End point title | Vital signs change from baseline : weight |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

12 months

| End point values | Placebo | Folinic acid: FA | L-thyroxin | FA + L-thyroxin |
|--------------------------------------|--------------------|--------------------|--------------------|--------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 40 | 30 | 35 | 38 |
| Units: Kg | | | | |
| arithmetic mean (standard deviation) | 2.13 (\pm 0.85) | 2.07 (\pm 0.72) | 2.23 (\pm 0.55) | 2.21 (\pm 0.88) |

Statistical analyses

No statistical analyses for this end point

Secondary: Vital signs change from baseline : Systolic blood pressure

| | |
|-----------------|--|
| End point title | Vital signs change from baseline : Systolic blood pressure |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

12 months

| End point values | Placebo | Folinic acid: FA | L-thyroxin | FA + L-thyroxin |
|--------------------------------------|---------------------|---------------------|---------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 40 | 30 | 34 | 38 |
| Units: mmHg | | | | |
| arithmetic mean (standard deviation) | 3.55 (\pm 13.32) | 4.13 (\pm 16.60) | 6.44 (\pm 13.29) | 5.21 (\pm 13.94) |

Statistical analyses

No statistical analyses for this end point

Secondary: Vital signs change from baseline : Diastolic blood pressure

| | |
|-----------------|---|
| End point title | Vital signs change from baseline : Diastolic blood pressure |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

12 months

| End point values | Placebo | Folinic acid: FA | L-thyroxin | FA + L-thyroxin |
|--------------------------------------|-----------------|------------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 40 | 30 | 34 | 38 |
| Units: mmHg | | | | |
| arithmetic mean (standard deviation) | 4.43 (± 14.74) | 6.17 (± 15.45) | 8.18 (± 13.70) | 5.63 (± 12.79) |

Statistical analyses

No statistical analyses for this end point

Secondary: Vital signs change from baseline : Heart rate

| | |
|------------------------|---|
| End point title | Vital signs change from baseline : Heart rate |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 12 months | |

| End point values | Placebo | Folinic acid: FA | L-thyroxin | FA + L-thyroxin |
|--------------------------------------|-----------------|------------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 40 | 30 | 34 | 38 |
| Units: bpm | | | | |
| arithmetic mean (standard deviation) | -9.70 (± 19.07) | -7.30 (± 19.11) | -5.82 (± 21.25) | 0.32 (± 21.98) |

Statistical analyses

No statistical analyses for this end point

Secondary: Safety TEAEs leading to death

| | |
|------------------------|-------------------------------|
| End point title | Safety TEAEs leading to death |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 12 months | |

| | | | | |
|------------------------------|----------------------|--|--|--|
| End point values | Safety | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 174 | | | |
| Units: count of participants | 1 | | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Clinical global impression (CGI)

| | |
|---|----------------------------------|
| End point title | Clinical global impression (CGI) |
| End point description: | |
| Overall evolution of CGI at Visit 3 from baseline | |
| End point type | Other pre-specified |
| End point timeframe: | |
| 12 months | |

| | | | | |
|------------------------------|-----------------|------------------|-----------------|-----------------|
| End point values | Placebo | Folinic acid: FA | L-thyroxin | FA + L-thyroxin |
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 40 | 30 | 35 | 38 |
| Units: count of participants | | | | |
| No progress | 2 | 1 | 0 | 0 |
| Slight progress | 27 | 16 | 22 | 18 |
| Marked progress | 11 | 13 | 12 | 20 |
| Very marked progress | 0 | 0 | 1 | 0 |

| | | | | |
|------------------------------|----------------------|--|--|--|
| End point values | mITT | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 143 | | | |
| Units: count of participants | | | | |
| No progress | 3 | | | |
| Slight progress | 83 | | | |
| Marked progress | 56 | | | |
| Very marked progress | 1 | | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Correlations between GMDS and BL-R GDQ

| | |
|--|--|
| End point title | Correlations between GMDS and BL-R GDQ |
| End point description: Correlations between GMDS and BL/R GDQ values at Visits 2 and 3 and between changes from baseline in GMDS and BL/R GDQ at Visits 2 and 3 | |
| End point type | Other pre-specified |
| End point timeframe: 12 months | |

| End point values | Placebo | Folinic acid: FA | L-thyroxin | FA + L-thyroxin |
|----------------------------------|---------------------|---------------------|---------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 40 | 30 | 35 | 38 |
| Units: Correlation coefficient | | | | |
| number (confidence interval 95%) | 0.94 (0.89 to 0.97) | 0.93 (0.86 to 0.97) | 0.93 (0.85 to 0.96) | 0.93 (0.90 to 0.95) |

Statistical analyses

No statistical analyses for this end point

Post-hoc: Change from baseline in Free T4

| | |
|-----------------------------------|---------------------------------|
| End point title | Change from baseline in Free T4 |
| End point description: | |
| End point type | Post-hoc |
| End point timeframe: 12 months | |

| End point values | Placebo | Folinic acid: FA | L-thyroxin | FA + L-thyroxin |
|--------------------------------------|-----------------|------------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 40 | 29 | 34 | 38 |
| Units: pmol/L | | | | |
| arithmetic mean (standard deviation) | -0.48 (± 2.25) | -1.18 (± 2.09) | 2.92 (± 3.08) | 2.47 (± 3.76) |

Statistical analyses

No statistical analyses for this end point

Post-hoc: Change from baseline in TSH

| | |
|-----------------|-----------------------------|
| End point title | Change from baseline in TSH |
|-----------------|-----------------------------|

End point description:

| | |
|----------------|----------|
| End point type | Post-hoc |
|----------------|----------|

End point timeframe:

12 months

| End point values | Placebo | Folinic acid: FA | L-thyroxin | FA + L-thyroxin |
|--------------------------------------|-----------------|------------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 40 | 30 | 35 | 38 |
| Units: µU/mL | | | | |
| arithmetic mean (standard deviation) | 0.52 (± 2.01) | -0.54 (± 1.98) | -1.96 (± 1.56) | -1.91 (± 2.14) |

Statistical analyses

No statistical analyses for this end point

Post-hoc: Change from baseline in Total Folates

| | |
|-----------------|---------------------------------------|
| End point title | Change from baseline in Total Folates |
|-----------------|---------------------------------------|

End point description:

| | |
|----------------|----------|
| End point type | Post-hoc |
|----------------|----------|

End point timeframe:

12 months

| End point values | Placebo | Folinic acid: FA | L-thyroxin | FA + L-thyroxin |
|--------------------------------------|------------------|--------------------|------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 14 | 15 | 12 | 17 |
| Units: nmol/L | | | | |
| arithmetic mean (standard deviation) | -20.25 (± 23.39) | 1288.98 (± 898.78) | -13.01 (± 19.43) | 2569.53 (± 5318.28) |

Statistical analyses

No statistical analyses for this end point

Post-hoc: Change from baseline in Homocysteine

| | |
|-----------------|--------------------------------------|
| End point title | Change from baseline in Homocysteine |
|-----------------|--------------------------------------|

End point description:

| | |
|----------------|----------|
| End point type | Post-hoc |
|----------------|----------|

End point timeframe:

12 months

| End point values | Placebo | Folinic acid: FA | L-thyroxin | FA + L-thyroxin |
|--------------------------------------|---------------------|---------------------|--------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 34 | 27 | 31 | 31 |
| Units: $\mu\text{mol/L}$ | | | | |
| arithmetic mean (standard deviation) | -0.19 (\pm 1.40) | -0.71 (\pm 1.29) | 0.14 (\pm 1.47) | -1.09 (\pm 2.74) |

Statistical analyses

No statistical analyses for this end point

Post-hoc: Change from baseline in S-Adenosyl Methionine

| | |
|-----------------|---|
| End point title | Change from baseline in S-Adenosyl Methionine |
|-----------------|---|

End point description:

| | |
|----------------|----------|
| End point type | Post-hoc |
|----------------|----------|

End point timeframe:

12 months

| End point values | Placebo | Folinic acid: FA | L-thyroxin | FA + L-thyroxin |
|--------------------------------------|----------------------|----------------------|-----------------------|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 34 | 27 | 31 | 31 |
| Units: nmol/L | | | | |
| arithmetic mean (standard deviation) | -8.32 (\pm 19.81) | 16.83 (\pm 26.20) | -12.30 (\pm 23.52) | 14.63 (\pm 38.03) |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

pneumonia viral 12 months

Adverse event reporting additional description:

Adverse event assessment was to be performed throughout the study. AEs occurring after the end of this observation period were to be reported by the investigator if he/she considered that there was a causal relationship with the study product. Standard AE definitions, monitoring and reporting were used.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 20.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

double placebo: Thyroxin placebo+ folinic acid placebo

| | |
|-----------------------|------------------|
| Reporting group title | Folinic acid: FA |
|-----------------------|------------------|

Reporting group description:

folinic acid + L-thyroxin placebo

| | |
|-----------------------|------------|
| Reporting group title | L-thyroxin |
|-----------------------|------------|

Reporting group description:

L-thyroxin+ folinic acid placebo

| | |
|-----------------------|-----------------|
| Reporting group title | FA + L-thyroxin |
|-----------------------|-----------------|

Reporting group description:

folinic acid + L-thyroxin

| Serious adverse events | Placebo | Folinic acid: FA | L-thyroxin |
|---|-----------------|------------------|-----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 5 / 44 (11.36%) | 8 / 43 (18.60%) | 9 / 44 (20.45%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Acute myeloid leukaemia | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 43 (2.33%) | 0 / 44 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Burns second degree | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 43 (2.33%) | 0 / 44 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Congenital, familial and genetic disorders | | | |
| Cryptorchism | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |
| Hernia diaphragmatic repair | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 43 (2.33%) | 0 / 44 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lacrimal duct procedure | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Adenoidectomy | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Infantile spasms | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 43 (2.33%) | 0 / 44 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 43 (2.33%) | 0 / 44 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sudden death | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Lung disorder | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 2 / 43 (4.65%) | 1 / 44 (2.27%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Asthmatic crisis | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 43 (2.33%) | 2 / 44 (4.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Asthma | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Adenoidal hypertrophy | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 43 (2.33%) | 0 / 44 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Choking | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| INFANTILE ASTHMA | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Interstitial lung disease | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tonsillar hypertrophy | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 43 (2.33%) | 0 / 44 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Acute haemorrhagic oedema of infancy | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 2 / 44 (4.55%) | 1 / 43 (2.33%) | 0 / 44 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchiolitis | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 43 (2.33%) | 0 / 44 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory syncytial virus bronchiolitis | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Laryngitis | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Lung infection | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| OTITIS MEDIA ACUTE | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pharyngitis | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia viral | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 2 / 44 (4.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dehydration | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|--|--|
| Serious adverse events | FA + L-thyroxin | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 8 / 43 (18.60%) | | |
| number of deaths (all causes) | 1 | | |
| number of deaths resulting from adverse events | 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Acute myeloid leukaemia | | | |

| | | | |
|--|----------------|--|--|
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Burns second degree | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Congenital, familial and genetic disorders | | | |
| Cryptorchism | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Surgical and medical procedures | | | |
| Hernia diaphragmatic repair | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lacrimal duct procedure | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Adenoidectomy | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Infantile spasms | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sudden death | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Lung disorder | | | |
| subjects affected / exposed | 2 / 43 (4.65%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Asthmatic crisis | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Asthma | | | |
| subjects affected / exposed | 2 / 43 (4.65%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Adenoidal hypertrophy | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Choking | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| INFANTILE ASTHMA | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Interstitial lung disease | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tonsillar hypertrophy | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Acute haemorrhagic oedema of infancy | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 2 / 43 (4.65%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bronchiolitis | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory syncytial virus bronchiolitis | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|----------------|--|--|
| Laryngitis | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lung infection | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| OTITIS MEDIA ACUTE | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia viral | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | Placebo | Folinic acid: FA | L-thyroxin |
|--|-------------------|------------------|------------------|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 44 / 44 (100.00%) | 38 / 43 (88.37%) | 36 / 44 (81.82%) |
| Surgical and medical procedures | | | |
| Adenoidectomy | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Middle ear prosthesis insertion | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 43 (2.33%) | 0 / 44 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Rhinitis prophylaxis | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences (all) | 0 | 0 | 1 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 12 / 44 (27.27%) | 15 / 43 (34.88%) | 11 / 44 (25.00%) |
| occurrences (all) | 20 | 16 | 13 |
| Crying | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| OEDEMA | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Immune system disorders | | | |
| Allergy to arthropod sting | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 43 (2.33%) | 0 / 44 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 8 / 44 (18.18%) | 4 / 43 (9.30%) | 5 / 44 (11.36%) |
| occurrences (all) | 10 | 4 | 8 |
| Lung disorder | | | |

| | | | |
|----------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 2 / 44 (4.55%) | 1 / 43 (2.33%) | 2 / 44 (4.55%) |
| occurrences (all) | 3 | 2 | 2 |
| Asthma | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 3 / 43 (6.98%) | 2 / 44 (4.55%) |
| occurrences (all) | 1 | 6 | 2 |
| Bronchial obstruction | | | |
| subjects affected / exposed | 3 / 44 (6.82%) | 1 / 43 (2.33%) | 2 / 44 (4.55%) |
| occurrences (all) | 5 | 2 | 3 |
| ASTHMATIC CRISIS | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences (all) | 1 | 0 | 2 |
| Sleep apnoea syndrome | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 2 / 44 (4.55%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Obstructive airways disorder | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences (all) | 0 | 0 | 1 |
| Rhinitis allergic | | | |
| subjects affected / exposed | 2 / 44 (4.55%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Alveolitis | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences (all) | 0 | 0 | 1 |
| Increased upper airway secretion | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences (all) | 0 | 0 | 1 |
| Nasal obstruction | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 43 (2.33%) | 0 / 44 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Rhinorrhoea | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences (all) | 0 | 0 | 1 |
| Stridor | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences (all) | 0 | 0 | 1 |
| Upper airway obstruction | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Adenoidal hypertrophy | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| infantile asthma | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Psychiatric disorders | | | |
| Agitation | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Insomnia | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Investigations | | | |
| Neutrophil count abnormal | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 1 / 43 (2.33%) | 0 / 44 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Serum ferritin decreased | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences (all) | 0 | 0 | 1 |
| Sleep study abnormal | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 43 (2.33%) | 0 / 44 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| Clavicle fracture subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 1 / 43 (2.33%) 1 | 0 / 44 (0.00%) 0 |
| Craniocerebral injury subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 0 / 43 (0.00%) 0 | 0 / 44 (0.00%) 0 |
| Lip injury subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 0 / 43 (0.00%) 0 | 1 / 44 (2.27%) 1 |
| Congenital, familial and genetic disorders Atrial septal defect subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 0 / 43 (0.00%) 0 | 0 / 44 (0.00%) 0 |
| Cardiac disorders Mitral valve incompetence subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 0 / 43 (0.00%) 0 | 0 / 44 (0.00%) 0 |
| Pericardial effusion subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 0 / 43 (0.00%) 0 | 0 / 44 (0.00%) 0 |
| Tachycardia subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 1 / 43 (2.33%) 1 | 0 / 44 (0.00%) 0 |
| Nervous system disorders Infantile spasms subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 0 / 43 (0.00%) 0 | 1 / 44 (2.27%) 1 |
| Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 3 / 43 (6.98%) 3 | 2 / 44 (4.55%) 2 |
| Anaemia subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 0 / 43 (0.00%) 0 | 4 / 44 (9.09%) 4 |
| NEUTROPHILIA | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 44 (0.00%) | 2 / 43 (4.65%) | 1 / 44 (2.27%) |
| occurrences (all) | 0 | 2 | 2 |
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 1 / 43 (2.33%) | 1 / 44 (2.27%) |
| occurrences (all) | 1 | 1 | 1 |
| LEUKOPENIA | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 3 / 44 (6.82%) |
| occurrences (all) | 0 | 0 | 3 |
| Lymphopenia | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 43 (2.33%) | 2 / 44 (4.55%) |
| occurrences (all) | 0 | 1 | 2 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences (all) | 0 | 0 | 1 |
| Leukocytosis | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences (all) | 0 | 0 | 1 |
| Monocytosis | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences (all) | 0 | 0 | 1 |
| Thrombocytosis | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 43 (2.33%) | 0 / 44 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Ear and labyrinth disorders | | | |
| Ear congestion | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 43 (2.33%) | 1 / 44 (2.27%) |
| occurrences (all) | 0 | 1 | 1 |
| Deafness | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences (all) | 0 | 0 | 1 |
| Eye disorders | | | |
| Hypermetropia | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 43 (2.33%) | 3 / 44 (6.82%) |
| occurrences (all) | 0 | 1 | 3 |
| Astigmatism | | | |

| | | | |
|----------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences (all) | 1 | 0 | 1 |
| Strabismus | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences (all) | 1 | 0 | 1 |
| Chalazion | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences (all) | 0 | 0 | 1 |
| Keratitis | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences (all) | 0 | 0 | 1 |
| Myopia | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 9 / 44 (20.45%) | 7 / 43 (16.28%) | 7 / 44 (15.91%) |
| occurrences (all) | 9 | 8 | 7 |
| Diarrhoea | | | |
| subjects affected / exposed | 7 / 44 (15.91%) | 7 / 43 (16.28%) | 5 / 44 (11.36%) |
| occurrences (all) | 10 | 10 | 6 |
| Constipation | | | |
| subjects affected / exposed | 5 / 44 (11.36%) | 2 / 43 (4.65%) | 7 / 44 (15.91%) |
| occurrences (all) | 7 | 2 | 9 |
| Teething | | | |
| subjects affected / exposed | 4 / 44 (9.09%) | 3 / 43 (6.98%) | 4 / 44 (9.09%) |
| occurrences (all) | 4 | 4 | 7 |
| Vomiting | | | |
| subjects affected / exposed | 2 / 44 (4.55%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Abnormal faeces | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences (all) | 2 | 0 | 1 |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| | | | |
|--|----------------|----------------|----------------|
| Aphthous ulcer | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Faeces hard | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 43 (2.33%) | 0 / 44 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| FREQUENT BOWEL MOVEMENTS | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| STOMATITIS | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 4 / 44 (9.09%) | 3 / 43 (6.98%) | 4 / 44 (9.09%) |
| occurrences (all) | 5 | 3 | 5 |
| Eczema | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 43 (0.00%) | 2 / 44 (4.55%) |
| occurrences (all) | 1 | 0 | 2 |
| Urticaria | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 43 (2.33%) | 2 / 44 (4.55%) |
| occurrences (all) | 0 | 2 | 2 |
| Purpura | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences (all) | 0 | 0 | 1 |
| Dermatitis diaper | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dry skin | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Petechiae | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences (all) | 0 | 0 | 1 |
| Prurigo | | | |

| | | | |
|---|------------------------|------------------------|------------------------|
| subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 0 / 43 (0.00%) 0 | 1 / 44 (2.27%) 1 |
| Rosacea subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 0 / 43 (0.00%) 0 | 0 / 44 (0.00%) 0 |
| Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 5 / 43 (11.63%) 5 | 0 / 44 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders Growth retardation subjects affected / exposed occurrences (all) | 0 / 44 (0.00%) 0 | 0 / 43 (0.00%) 0 | 0 / 44 (0.00%) 0 |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 21 / 44 (47.73%) 32 | 20 / 43 (46.51%) 31 | 15 / 44 (34.09%) 30 |
| Ear infection subjects affected / exposed occurrences (all) | 19 / 44 (43.18%) 25 | 13 / 43 (30.23%) 24 | 14 / 44 (31.82%) 26 |
| Rhinitis subjects affected / exposed occurrences (all) | 16 / 44 (36.36%) 23 | 9 / 43 (20.93%) 14 | 17 / 44 (38.64%) 22 |
| Bronchitis subjects affected / exposed occurrences (all) | 15 / 44 (34.09%) 25 | 8 / 43 (18.60%) 11 | 13 / 44 (29.55%) 23 |
| Gastroenteritis subjects affected / exposed occurrences (all) | 12 / 44 (27.27%) 16 | 13 / 43 (30.23%) 17 | 13 / 44 (29.55%) 13 |
| Conjunctivitis subjects affected / exposed occurrences (all) | 14 / 44 (31.82%) 18 | 7 / 43 (16.28%) 8 | 12 / 44 (27.27%) 21 |
| Bronchiolitis subjects affected / exposed occurrences (all) | 10 / 44 (22.73%) 11 | 7 / 43 (16.28%) 12 | 9 / 44 (20.45%) 10 |
| Tonsillitis | | | |

| | | | |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 5 / 44 (11.36%) | 2 / 43 (4.65%) | 8 / 44 (18.18%) |
| occurrences (all) | 5 | 2 | 10 |
| varicella | | | |
| subjects affected / exposed | 3 / 44 (6.82%) | 8 / 43 (18.60%) | 8 / 44 (18.18%) |
| occurrences (all) | 3 | 9 | 8 |
| Laryngitis | | | |
| subjects affected / exposed | 2 / 44 (4.55%) | 7 / 43 (16.28%) | 7 / 44 (15.91%) |
| occurrences (all) | 2 | 14 | 10 |
| Otitis media | | | |
| subjects affected / exposed | 3 / 44 (6.82%) | 3 / 43 (6.98%) | 5 / 44 (11.36%) |
| occurrences (all) | 5 | 4 | 5 |
| HAND-FOOT-AND-MOUTH DISEASE | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 2 / 43 (4.65%) | 3 / 44 (6.82%) |
| occurrences (all) | 1 | 2 | 3 |
| Influenza | | | |
| subjects affected / exposed | 4 / 44 (9.09%) | 3 / 43 (6.98%) | 0 / 44 (0.00%) |
| occurrences (all) | 5 | 4 | 0 |
| Viral infection | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 2 / 43 (4.65%) | 2 / 44 (4.55%) |
| occurrences (all) | 1 | 2 | 2 |
| Pharyngitis | | | |
| subjects affected / exposed | 2 / 44 (4.55%) | 0 / 43 (0.00%) | 3 / 44 (6.82%) |
| occurrences (all) | 4 | 0 | 3 |
| Roseola | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 2 / 43 (4.65%) | 1 / 44 (2.27%) |
| occurrences (all) | 1 | 2 | 1 |
| Oral candidiasis | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 1 / 43 (2.33%) | 2 / 44 (4.55%) |
| occurrences (all) | 2 | 2 | 2 |
| SCARLET FEVER | | | |
| subjects affected / exposed | 2 / 44 (4.55%) | 1 / 43 (2.33%) | 2 / 44 (4.55%) |
| occurrences (all) | 2 | 1 | 2 |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 44 (4.55%) | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences (all) | 2 | 0 | 2 |
| Oral fungal infection | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 2 / 44 (4.55%) | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences (all) | 3 | 0 | 1 |
| Oral herpes | | | |
| subjects affected / exposed | 2 / 44 (4.55%) | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences (all) | 2 | 0 | 1 |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences (all) | 0 | 0 | 2 |
| FUNGAL INFECTION | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 1 / 43 (2.33%) | 0 / 44 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Respiratory syncytial virus bronchiolitis | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences (all) | 0 | 0 | 1 |
| Tracheitis | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 2 / 43 (4.65%) | 0 / 44 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| UPPER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences (all) | 0 | 0 | 1 |
| Paronychia | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 43 (2.33%) | 1 / 44 (2.27%) |
| occurrences (all) | 0 | 1 | 1 |
| Abscess oral | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 43 (2.33%) | 0 / 44 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Candida nappy rash | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 43 (2.33%) | 0 / 44 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Coxsackie viral infection | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| CYTOMEGALOVIRUS INFECTION | | | |

| | | | |
|------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences (all) | 0 | 0 | 1 |
| ENTEROBIASIS | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Erythema infectiosum | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hordeolum | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 43 (2.33%) | 0 / 44 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Infection | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pneumonia mycoplasmal | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Purulent discharge | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rhinotracheitis | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin infection | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences (all) | 0 | 0 | 1 |
| Tonsillitis bacterial | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| TRACHEOBRONCHITIS | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Viral rash | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 0 / 43 (0.00%) | 0 / 44 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Viral tonsillitis | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 1 / 44 (2.27%) 1 | 0 / 43 (0.00%) 0 | 0 / 44 (0.00%) 0 |
| Metabolism and nutrition disorders | | | |
| Iron deficiency | | | |
| subjects affected / exposed | 3 / 44 (6.82%) | 6 / 43 (13.95%) | 6 / 44 (13.64%) |
| occurrences (all) | 3 | 7 | 6 |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 0 / 43 (0.00%) | 1 / 44 (2.27%) |
| occurrences (all) | 0 | 0 | 1 |
| Weight gain poor | | | |
| subjects affected / exposed | 1 / 44 (2.27%) | 1 / 43 (2.33%) | 0 / 44 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Dehydration | | | |
| subjects affected / exposed | 0 / 44 (0.00%) | 1 / 43 (2.33%) | 0 / 44 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|---|------------------|--|--|
| Non-serious adverse events | FA + L-thyroxin | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 40 / 43 (93.02%) | | |
| Surgical and medical procedures | | | |
| Adenoidectomy | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Middle ear prosthesis insertion | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Rhinitis prophylaxis | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 14 / 43 (32.56%) | | |
| occurrences (all) | 30 | | |
| Crying | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| OEDEMA | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Immune system disorders | | | |
| Allergy to arthropod sting | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 4 / 43 (9.30%) | | |
| occurrences (all) | 4 | | |
| Lung disorder | | | |
| subjects affected / exposed | 3 / 43 (6.98%) | | |
| occurrences (all) | 5 | | |
| Asthma | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Bronchial obstruction | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| ASTHMATIC CRISIS | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Sleep apnoea syndrome | | | |
| subjects affected / exposed | 3 / 43 (6.98%) | | |
| occurrences (all) | 3 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Obstructive airways disorder | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 2 | | |
| Rhinitis allergic | | | |

| | | | |
|----------------------------------|----------------|--|--|
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Alveolitis | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Increased upper airway secretion | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nasal obstruction | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Stridor | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Upper airway obstruction | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Adenoidal hypertrophy | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| infantile asthma | | | |
| subjects affected / exposed | 2 / 43 (4.65%) | | |
| occurrences (all) | 2 | | |
| Psychiatric disorders | | | |
| Agitation | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Insomnia | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |

| | | | |
|---|---------------------|--|--|
| Investigations | | | |
| Neutrophil count abnormal subjects affected / exposed occurrences (all) | 0 / 43 (0.00%) 0 | | |
| Serum ferritin decreased subjects affected / exposed occurrences (all) | 0 / 43 (0.00%) 0 | | |
| Sleep study abnormal subjects affected / exposed occurrences (all) | 0 / 43 (0.00%) 0 | | |
| Weight decreased subjects affected / exposed occurrences (all) | 1 / 43 (2.33%) 1 | | |
| Injury, poisoning and procedural complications | | | |
| Clavicle fracture subjects affected / exposed occurrences (all) | 0 / 43 (0.00%) 0 | | |
| Craniocerebral injury subjects affected / exposed occurrences (all) | 0 / 43 (0.00%) 0 | | |
| Lip injury subjects affected / exposed occurrences (all) | 0 / 43 (0.00%) 0 | | |
| Congenital, familial and genetic disorders | | | |
| Atrial septal defect subjects affected / exposed occurrences (all) | 1 / 43 (2.33%) 2 | | |
| Cardiac disorders | | | |
| Mitral valve incompetence subjects affected / exposed occurrences (all) | 1 / 43 (2.33%) 1 | | |
| Pericardial effusion subjects affected / exposed occurrences (all) | 1 / 43 (2.33%) 2 | | |
| Tachycardia | | | |

| | | | |
|---|---------------------|--|--|
| subjects affected / exposed occurrences (all) | 0 / 43 (0.00%) 0 | | |
| Nervous system disorders Infantile spasms subjects affected / exposed occurrences (all) | 0 / 43 (0.00%) 0 | | |
| Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all) | 2 / 43 (4.65%) 2 | | |
| Anaemia subjects affected / exposed occurrences (all) | 0 / 43 (0.00%) 0 | | |
| NEUTROPHILIA subjects affected / exposed occurrences (all) | 2 / 43 (4.65%) 2 | | |
| Iron deficiency anaemia subjects affected / exposed occurrences (all) | 1 / 43 (2.33%) 1 | | |
| LEUKOPENIA subjects affected / exposed occurrences (all) | 0 / 43 (0.00%) 0 | | |
| Lymphopenia subjects affected / exposed occurrences (all) | 0 / 43 (0.00%) 0 | | |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 2 / 43 (4.65%) 2 | | |
| Leukocytosis subjects affected / exposed occurrences (all) | 0 / 43 (0.00%) 0 | | |
| Monocytosis subjects affected / exposed occurrences (all) | 0 / 43 (0.00%) 0 | | |
| Thrombocytosis | | | |

| | | | |
|--|---------------------|--|--|
| subjects affected / exposed occurrences (all) | 0 / 43 (0.00%) 0 | | |
| Ear and labyrinth disorders | | | |
| Ear congestion | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Deafness | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Eye disorders | | | |
| Hypermetropia | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Astigmatism | | | |
| subjects affected / exposed | 2 / 43 (4.65%) | | |
| occurrences (all) | 2 | | |
| Strabismus | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Chalazion | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Keratitis | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Myopia | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gastrointestinal disorders | | | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 8 / 43 (18.60%) | | |
| occurrences (all) | 9 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 8 / 43 (18.60%) | | |
| occurrences (all) | 8 | | |
| Constipation | | | |

| | | | |
|--|-----------------|--|--|
| subjects affected / exposed | 3 / 43 (6.98%) | | |
| occurrences (all) | 3 | | |
| Teething | | | |
| subjects affected / exposed | 6 / 43 (13.95%) | | |
| occurrences (all) | 19 | | |
| Vomiting | | | |
| subjects affected / exposed | 3 / 43 (6.98%) | | |
| occurrences (all) | 3 | | |
| Abnormal faeces | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Aphthous ulcer | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Faeces hard | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| FREQUENT BOWEL MOVEMENTS | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| STOMATITIS | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 2 | | |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 5 / 43 (11.63%) | | |
| occurrences (all) | 7 | | |
| Eczema | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Urticaria | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |

| | | | |
|---|------------------------|--|--|
| Purpura subjects affected / exposed occurrences (all) | 1 / 43 (2.33%) 1 | | |
| Dermatitis diaper subjects affected / exposed occurrences (all) | 1 / 43 (2.33%) 2 | | |
| Dry skin subjects affected / exposed occurrences (all) | 0 / 43 (0.00%) 0 | | |
| Petechiae subjects affected / exposed occurrences (all) | 0 / 43 (0.00%) 0 | | |
| Prurigo subjects affected / exposed occurrences (all) | 0 / 43 (0.00%) 0 | | |
| Rosacea subjects affected / exposed occurrences (all) | 1 / 43 (2.33%) 1 | | |
| Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all) | 0 / 43 (0.00%) 0 | | |
| Musculoskeletal and connective tissue disorders Growth retardation subjects affected / exposed occurrences (all) | 1 / 43 (2.33%) 1 | | |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 16 / 43 (37.21%) 22 | | |
| Ear infection subjects affected / exposed occurrences (all) | 21 / 43 (48.84%) 48 | | |
| Rhinitis subjects affected / exposed occurrences (all) | 17 / 43 (39.53%) 25 | | |

| | | | |
|-----------------------------|------------------|--|--|
| Bronchitis | | | |
| subjects affected / exposed | 17 / 43 (39.53%) | | |
| occurrences (all) | 25 | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 10 / 43 (23.26%) | | |
| occurrences (all) | 13 | | |
| Conjunctivitis | | | |
| subjects affected / exposed | 14 / 43 (32.56%) | | |
| occurrences (all) | 19 | | |
| Bronchiolitis | | | |
| subjects affected / exposed | 11 / 43 (25.58%) | | |
| occurrences (all) | 17 | | |
| Tonsillitis | | | |
| subjects affected / exposed | 13 / 43 (30.23%) | | |
| occurrences (all) | 21 | | |
| varicella | | | |
| subjects affected / exposed | 8 / 43 (18.60%) | | |
| occurrences (all) | 8 | | |
| Laryngitis | | | |
| subjects affected / exposed | 6 / 43 (13.95%) | | |
| occurrences (all) | 6 | | |
| Otitis media | | | |
| subjects affected / exposed | 5 / 43 (11.63%) | | |
| occurrences (all) | 5 | | |
| HAND-FOOT-AND-MOUTH DISEASE | | | |
| subjects affected / exposed | 4 / 43 (9.30%) | | |
| occurrences (all) | 4 | | |
| Influenza | | | |
| subjects affected / exposed | 3 / 43 (6.98%) | | |
| occurrences (all) | 3 | | |
| Viral infection | | | |
| subjects affected / exposed | 5 / 43 (11.63%) | | |
| occurrences (all) | 5 | | |
| Pharyngitis | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |

| | | | |
|--|----------------|--|--|
| Roseola | | | |
| subjects affected / exposed | 3 / 43 (6.98%) | | |
| occurrences (all) | 3 | | |
| Oral candidiasis | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| SCARLET FEVER | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Oral fungal infection | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Oral herpes | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| FUNGAL INFECTION | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Respiratory syncytial virus bronchiolitis | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Tracheitis | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| UPPER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 2 / 43 (4.65%) | | |
| occurrences (all) | 4 | | |
| Paronychia | | | |

| | | | |
|-----------------------------|----------------|--|--|
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Abscess oral | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Candida nappy rash | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Coxsackie viral infection | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| CYTOMEGALOVIRUS INFECTION | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| ENTEROBIASIS | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Erythema infectiosum | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Hordeolum | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Infection | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pneumonia mycoplasmal | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Purulent discharge | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Rhinotracheitis | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Skin infection | | | |

| | | | |
|------------------------------------|-----------------|--|--|
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Tonsillitis bacterial | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| TRACHEOBRONCHITIS | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Viral rash | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Viral tonsillitis | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |
| Metabolism and nutrition disorders | | | |
| Iron deficiency | | | |
| subjects affected / exposed | 7 / 43 (16.28%) | | |
| occurrences (all) | 7 | | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Weight gain poor | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences (all) | 1 | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences (all) | 0 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 13 July 2012 | Protocol version #11 (Amendment #1) Modification of inclusion criteria, addition of withdrawal criterion |
| 09 October 2012 | Protocol version #12 (Amendment #2) Protocol version #11 (13 July 2012) renumbered version # 12 after approval by EC/HA 09 October 2012 (no change to protocol) |
| 26 November 2013 | Protocol version #13 (Amendment #3) Modification of inclusion/exclusion criteria, removal of endpoint, clarification of sample collection, stopping rule, and follow-up |
| 06 March 2014 | Protocol version #13 (Amendment #4) Modified list of investigators only (no change to protocol) |
| 13 October 2014 | Protocol version #15 (Amendment #5) Modification of inclusion criterion, clarification of SAE reporting |
| 09 June 2015 | Protocol version #15 (Amendment #6) Modified list of investigators only (no change to protocol) |
| 12 June 2015 | Protocol version #16 (Amendment #7) Change in sample size and addition of a second interim analysis |
| 13 November 2015 | Protocol version #17 (Amendment #8) Change in sample size and removal of both interim analyses; modification of statistical methodology |
| 20 July 2017 | Protocol version #19 (Amendment #9) Specification of genomic analyses, addition of creatine dosing, modified list of investigators |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported