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 Synopis (_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			
Atrioventicular septal defect (AVSD) YES for subjects with Atrioventicular septal defect			

Atrioventicular septal defect (AVSD) NO for subjects without Atrioventicular septal defect			
Units: Subjects			
Atrioventicular septal defect (AVSD) YES	2	1	1
Atrioventicular 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 prolaspse (except AVSD) YES for subjects with Mitral valve prolaspse (except AVSD) Mitral valve prolaspse (except AVSD) NO for subjects withouth Mitral valve prolaspse (except AVSD)			
Units: Subjects			
Mitral valve prolaspse (except AVSD) YES	0	0	0
Mitral valve prolaspse (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			
Atrioventicular septal defect (AVSD) YES for subjects with Atrioventicular septal defect Atrioventicular septal defect (AVSD) NO for subjects without Atrioventicular septal defect			
Units: Subjects			
Atrioventicular septal defect (AVSD) YES	2	6	

Atrioventicular 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 withouth 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			
Atrioventicular septal defect (AVSD) YES for subjects with Atrioventicular septal defect Atrioventicular septal defect (AVSD) NO for subjects without Atrioventicular septal defect			
Units: Subjects			
Atrioventicular septal defect (AVSD) YES			
Atrioventicular 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 prolaspse (except AVSD) YES for subjects with Mitral valve prolaspse (except AVSD) Mitral valve prolaspse (except AVSD) NO for subjects withouth Mitral valve prolaspse (except AVSD)			
Units: Subjects			
Mitral valve prolaspse (except AVSD) YES			

Mitral valve prolaspse (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			
Atrioventicular septal defect (AVSD) YES for subjects with Atrioventicular septal defect Atrioventicular septal defect (AVSD) NO for subjects without Atrioventicular septal defect			
Units: Subjects			
Atrioventicular septal defect (AVSD) YES Atrioventicular 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 prolaspse (except AVSD) YES for subjects with Mitral valve prolaspse (except AVSD) Mitral valve prolaspse (except AVSD) NO for subjects withouth Mitral valve prolaspse (except AVSD)			
Units: Subjects			
Mitral valve prolaspse (except AVSD) YES Mitral valve prolaspse (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+ 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	
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 (± 0.85)	2.07 (± 0.72)	2.23 (± 0.55)	2.21 (± 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 (± 13.32)	4.13 (± 16.60)	6.44 (± 13.29)	5.21 (± 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: µmol/L				
arithmetic mean (standard deviation)	-0.19 (± 1.40)	-0.71 (± 1.29)	0.14 (± 1.47)	-1.09 (± 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 (± 19.81)	16.83 (± 26.20)	-12.30 (± 23.52)	14.63 (± 38.03)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

pneumonia viral12 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	0 / 44 (0.00%)	1 / 43 (2.33%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Craniocerebral injury			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	0
Lip injury			
subjects affected / exposed	0 / 44 (0.00%)	0 / 43 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Congenital, familial and genetic disorders			
Atrial septal defect			
subjects affected / exposed	0 / 44 (0.00%)	0 / 43 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Mitral valve incompetence			
subjects affected / exposed	0 / 44 (0.00%)	0 / 43 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Pericardial effusion			
subjects affected / exposed	0 / 44 (0.00%)	0 / 43 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Tachycardia			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	0 / 44 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Infantile spasms			
subjects affected / exposed	0 / 44 (0.00%)	0 / 43 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 44 (2.27%)	3 / 43 (6.98%)	2 / 44 (4.55%)
occurrences (all)	1	3	2
Anaemia			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	4 / 44 (9.09%)
occurrences (all)	1	0	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	0 / 44 (0.00%)	0 / 43 (0.00%)	1 / 44 (2.27%)
occurrences (all)	0	0	1
Rosacea			
subjects affected / exposed	0 / 44 (0.00%)	0 / 43 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 44 (0.00%)	5 / 43 (11.63%)	0 / 44 (0.00%)
occurrences (all)	0	5	0
Musculoskeletal and connective tissue disorders			
Growth retardation			
subjects affected / exposed	0 / 44 (0.00%)	0 / 43 (0.00%)	0 / 44 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	21 / 44 (47.73%)	20 / 43 (46.51%)	15 / 44 (34.09%)
occurrences (all)	32	31	30
Ear infection			
subjects affected / exposed	19 / 44 (43.18%)	13 / 43 (30.23%)	14 / 44 (31.82%)
occurrences (all)	25	24	26
Rhinitis			
subjects affected / exposed	16 / 44 (36.36%)	9 / 43 (20.93%)	17 / 44 (38.64%)
occurrences (all)	23	14	22
Bronchitis			
subjects affected / exposed	15 / 44 (34.09%)	8 / 43 (18.60%)	13 / 44 (29.55%)
occurrences (all)	25	11	23
Gastroenteritis			
subjects affected / exposed	12 / 44 (27.27%)	13 / 43 (30.23%)	13 / 44 (29.55%)
occurrences (all)	16	17	13
Conjunctivitis			
subjects affected / exposed	14 / 44 (31.82%)	7 / 43 (16.28%)	12 / 44 (27.27%)
occurrences (all)	18	8	21
Bronchiolitis			
subjects affected / exposed	10 / 44 (22.73%)	7 / 43 (16.28%)	9 / 44 (20.45%)
occurrences (all)	11	12	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	1 / 44 (2.27%)	0 / 43 (0.00%)	0 / 44 (0.00%)
occurrences (all)	1	0	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	0 / 43 (0.00%)		
occurrences (all)	0		
Serum ferritin decreased			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Sleep study abnormal			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Weight decreased			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Craniocerebral injury			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Lip injury			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Congenital, familial and genetic disorders			
Atrial septal defect			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	2		
Cardiac disorders			
Mitral valve incompetence			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Pericardial effusion			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	2		
Tachycardia			

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

subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	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	1 / 43 (2.33%)		
occurrences (all)	1		
Dermatitis diaper			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	2		
Dry skin			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Petechiae			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Prurigo			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Rosacea			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Growth retardation			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	16 / 43 (37.21%)		
occurrences (all)	22		
Ear infection			
subjects affected / exposed	21 / 43 (48.84%)		
occurrences (all)	48		
Rhinitis			
subjects affected / exposed	17 / 43 (39.53%)		
occurrences (all)	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 occurrences (all)	0 / 43 (0.00%) 0		
Tonsillitis bacterial subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0		
TRACHEOBRONCHITIS subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1		
Viral rash subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0		
Viral tonsillitis subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0		
Metabolism and nutrition disorders			
Iron deficiency subjects affected / exposed occurrences (all)	7 / 43 (16.28%) 7		
Decreased appetite subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1		
Weight gain poor subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1		
Dehydration subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 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 byEC/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