Clinical trial results:
Evaluation of the efficiency of folinic acid in children with autism spectrum disorders: a pilot study "EFFET"

Summary

EudraCT number	2015-000955-25
Trial protocol	FR
Global end of trial date	31 August 2018

Results information

Result version number	v1 (current)
This version publication date	23 February 2023
First version publication date	23 February 2023
Summary attachment (see zip file)	EFFET_Article-Abstract (article effet biochimie 2019.pdf)

Trial information

Trial identification

Sponsor protocol code	PSS2015/EFFET-LEHEUP/SKJ

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02551380
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CHRU Nancy
Sponsor organisation address	Rue du MORVAN, Vandoeuvre les Nancy, France, 54511
Public contact	El Mehdi SIAGHY, Délégation à la Recherche clinique et à l'Innovation, 0033 383155285, dripromoteur@chru-nancy.fr
Scientific contact	El Mehdi SIAGHY, Délégation à la Recherche clinique et à l'Innovation, 0033 383155285, dripromoteur@chru-nancy.fr

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	31 December 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 August 2018
Global end of trial reached?	Yes
Global end of trial date	31 August 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study is to evaluate the efficiencyof folinic acid, as folinate calicum (FOLINORAL®) 5 mg two times a day during 12 weeks, on the reduction of autism disorder especially on the communication and social interactions.

Protection of trial subjects:

No specific protection mesures were set for the study

Background therapy:

No curative medical treatment are available in children with autism sprectrum disorders. Children beneficit of psychotherapy and reeducative care (speech therapy, psychomotricity...).

Evidence for comparator:

Placebo

Actual start date of recruitment	02 October 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Ethical reason, Regulatory reason, Scientific research
Long term follow-up duration	3 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 19
Worldwide total number of subjects	19
EEA total number of subjects	19

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)	0
Children (2-11 years)	19

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:

Date of start: 02/10/2015
Date of last visit of last participated patient: 31/08/2018
Place of recruitment: FRANCE/ CHRU Nancy/ Médecine infantile et génétique clinique

Pre-assignment

Screening details:

Children aged 3 to 10 years with autism spectrum disorders defined by : Autism Diagnostic Observation Schedule (ADOS), Autism Diagnostic Interview (ADI), Childhood Autism Rating Scale (CARS) or diagnosed by a physician (pediatrician, child psychiatrist)

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	folinic acid group

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Calcium Folinate, 5mg
Investigational medicinal product code	Marketing authorisation number: 3400933073770
Other name	FOLINORAL® or Calcium Folinate Pentahydrate
Pharmaceutical forms	Capsule, soft
Routes of administration	Buccal use

Dosage and administration details:

Calcium Folinate, 10 mg per day

Arm title	placebo group

Arm description:

Lactose

Arm type	Placebo
Investigational medicinal product name	lactose
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Buccal use

Dosage and administration details:

capsule of lactose twice a day

Number of subjects in period 1	folinic acid group	placebo group
Started	9	10
Completed	9	10

Baseline characteristics

Reporting groups	
Reporting group title	folinic acid group
Reporting group description: -	
Reporting group title	placebo group
Reporting group description:	
Lactose	

Reporting group values	folinic acid group	placebo group	Total
Number of subjects	9	10	19
Age categorical			
mean age of patient 6 years 2 months +/- 2 years old (min 3 years, max 10 years old)			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	9	10	19
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
children	0	0	0
Age continuous			
Units: months			
median	65.3	67.5	
standard deviation	± 27	± 28.8	-
Gender categorical			
4 girls et 15 boys			
Units: Subjects			
Female	3	1	4
Male	6	9	15
ADOS score			
ADOS score at baseline			
Units: points			
arithmetic mean	16.8	16.3	
standard deviation	± 4.4	± 3.2	-
SRS score at baseline			
Units: points			
arithmetic mean	92.2	93.4	
standard deviation	± 13.6	± 16	-
ADOS score Week 12			
Units: points			
arithmetic mean	14	15.9	
standard deviation	± 5	± 3.7	-
SRS score week 12			

Units: points			
arithmetic mean	83.9	85.5	
standard deviation	± 14.6	± 16.3	-
serum folates at weeks 12			
Units: nmol/L			
arithmetic mean	123.1	31.4	
standard deviation	± 83.3	± 31.2	-
Blocking FRA antibodies at T0			
Units: pmol/mL			
arithmetic mean	1	1.3	
standard deviation	± 2.2	± 2.1	-

Subject analysis sets

Subject analysis set title	XXX
Subject analysis set type	Full analysis

Subject analysis set description:

The analyses were conducted successively in intention-to-treat and per protocol.

Reporting group values	XXX		
Number of subjects	19		
Age categorical			
mean age of patient 6 years 2 months +/- 2 years old (min 3 years, max 10 years old)			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	19		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
children	0		
Age continuous			
Units: months			
median	66.3		
standard deviation	± 27.2		
Gender categorical			
4 girls et 15 boys			
Units: Subjects			
Female	4		
Male	15		
ADOS score			
ADOS score at baseline			
Units: points			
arithmetic mean	16,5		
standard deviation	± 3.7		
SRS score at baseline			
Units: points			

arithmetic mean	92.3		
standard deviation	± 14.5		
ADOS score Week 12			
Units: points			
arithmetic mean	15		
standard deviation	± 4.3		
SRS score week 12			
Units: points			
arithmetic mean	84.7		
standard deviation	± 15		
serum folates at weeks 12			
Units: nmol/L			
arithmetic mean	123		
standard deviation	± 83		
Blocking FRA antibodies at T0			
Units: pmol/mL			
arithmetic mean			
standard deviation	±		

End points

End points reporting groups	
Reporting group title	folinic acid group
Reporting group description: -	
Reporting group title	placebo group
Reporting group description: Lactose	
Subject analysis set title	XXX
Subject analysis set type	Full analysis
Subject analysis set description: The analyses were conducted successively in intention-to-treat and per protocol.	

Primary: ADOS score evolution	
End point title	ADOS score evolution
End point description:	
End point type	Primary
End point timeframe: ADOS score evolution between T0 and Week 12 of treatment	

End point values	folinic acid group	placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	10		
Units: points				
arithmetic mean (standard deviation)	-2.8 (± 1.9)	-0.4 (± 2.2)		

Statistical analyses

Statistical analysis title	statiscal comparison between groups
Comparison groups	folinic acid group v placebo group
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	t-test, 2-sided
Variability estimate	Standard deviation

Secondary: ADOS social interaction score evolution	
End point title	ADOS social interaction score evolution
End point description: in folinic acid group : mean score evolution -1.8 (1.3) versus 0.2 (0.2 sd) p= 0.19	

End point type	Secondary
End point timeframe: evolution between baseline and weeks 12 of treatment	

End point values	folinic acid group	placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	10		
Units: points				
arithmetic mean (standard deviation)	-1.8 (± 1.3)	0.2 (± 2.2)		

Statistical analyses

Statistical analysis title	statiscal comparison between groups
Comparison groups	folinic acid group v placebo group
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	t-test, 2-sided
Parameter estimate	Median difference (final values)
Variability estimate	Standard deviation

Secondary: ADOS communication score evolution	
End point title	ADOS communication score evolution
End point description: Mean ADOS communication score : in folinic acid group -1.2 (1.3 SD), versus in placebo group -0.4 (1.1sd) ; p =0.02	
End point type	Secondary
End point timeframe: between baseline T0 and W12	

End point values	folinic acid group	placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	10		
Units: points				
arithmetic mean (standard deviation)	-1.2 (± 1.3)	-0.4 (± 1.1)		

Statistical analyses

Statistical analysis title	statiscal comparison between groups
Comparison groups	folinic acid group v placebo group
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Variability estimate	Standard deviation

Secondary: SRS score evolution

End point title	SRS score evolution

End point description:

End point type	Secondary

End point timeframe:
between baseline T0 and W12

End point values	folinic acid group	placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	10		
Units: points				
arithmetic mean (standard deviation)	-8.3 (± 13.4)	-7.9 (± 12.7)		

Statistical analyses

Statistical analysis title	statiscal comparison between groups
Comparison groups	placebo group v folinic acid group
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Variability estimate	Standard deviation

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The AEs and SAEs were collected and reported to the sponsor from enrolment to the end of the study (week 24).

Adverse event reporting additional description:

Children's parents were contacted by telephone at 3 and 6 weeks after the start of the study to check for any adverse treatment effects and to verify compliance. Parents were provided with a telephone number for the principal investigator to report any adverse events.
A reassessment took place 12 weeks after the end of treatment (at week 24).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21

Reporting groups

Reporting group title	folinoral
Reporting group description: -	
Reporting group title	placebo

Reporting group description: -

Serious adverse events	folinoral	placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	folinoral	placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 10 (80.00%)	8 / 9 (88.89%)	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Vision blurred			

subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Constipation			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Asthmatic crisis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Epistaxis			
subjects affected / exposed	0 / 10 (0.00%)	2 / 9 (22.22%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 10 (20.00%)	2 / 9 (22.22%)	
occurrences (all)	2	2	
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
agression			
subjects affected / exposed	1 / 10 (10.00%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Sleep disorder			
subjects affected / exposed	1 / 10 (10.00%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
anger			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	

Musculoskeletal and connective tissue disorders			
Neck pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Infections and infestations			
Gastroenteritis viral			
subjects affected / exposed	1 / 10 (10.00%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Influenza			
subjects affected / exposed	1 / 10 (10.00%)	2 / 9 (22.22%)	
occurrences (all)	1	2	
Rhinolaryngitis			
subjects affected / exposed	2 / 10 (20.00%)	1 / 9 (11.11%)	
occurrences (all)	3	1	
Influenza like illness			
subjects affected / exposed	1 / 10 (10.00%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Otitis media			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 June 2016	Request for an additional 18-month extension of the inclusion period
07 February 2018	Request for an additional visit specific to the inclusion in the protocol when it is not possible to do so during the usual follow-up visit

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

-absence of double-blindness,
-carried out on a small number of children, a larger multicenter study over a longer period would be necessary.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/32387472