Clinical trial results:
Double-blind, randomised, placebo-controlled, parallel group study to evaluate the efficacy and safety of oral administration of Nepadutant in infant colic

Summary

EudraCT number	2009-018218-21
Trial protocol	DE SE
Global end of trial date	28 December 2013

Results information

Result version number	v1 (current)
This version publication date	04 November 2018
First version publication date	04 November 2018

Trial information

Trial identification

Sponsor protocol code	NIC-03

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01258153
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Menarini Ricerche S.p.A.
Sponsor organisation address	Via Sette Santi 1, Florence, Italy, 50131
Public contact	Angela Capriati, Menarini Ricerche S.p.A., +39 05556809990, acapriati@menarini-ricerche.it
Scientific contact	Angela Capriati, Menarini Ricerche S.p.A., +39 05556809990, acapriati@menarini-ricerche.it

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 October 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 December 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Efficacy of oral Nepadutant treatment given once daily at two doses in comparison to placebo

Protection of trial subjects:

Parents could withdraw consent for their baby participation in the study at any time without prejudice. The investigator could withdraw a subject if, in his/her clinical judgment, it was in the best interest of the subject or if the subject could not comply with the protocol.
The subject underwent to a final study visit (FU visit) after withdrawal, the cause of which had to be recorded in detail on the CRF/eCRF. If the withdrawal of a subject resulted from an adverse event, this was documented in accordance with procedures described under section "Adverse Event".

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 November 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	1 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	United States: 2
Country: Number of subjects enrolled	Russian Federation: 109
Worldwide total number of subjects	115
EEA total number of subjects	4

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)	115
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:

Screened patients were 130, of these, 15 were screening failures. Subjects randomised therefore were 115. Two patients were excluded from ITT population (n=113) due to: withdrawal of consent after 1st intake (1) and after 1 day with 0 intake.

Pre-assignment

Screening details:

Healthy infants(age >4 weeks and <20 weeks),breast-fed,mixed fed or formula fed with a stable dietary regimen,normal growth,infant colic as per modified Wessel criteria.At randomization,eligibility was confirmed by total of crying and/or fussing time lasting at least 6h during the last 3days screening SF:15;Main SF reason: I/E criteria not met(10)

Period 1

Period 1 title	Treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Data analyst, Carer, Assessor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Nepadutant low dose

Arm description:

Nepadutant oral solution 0.1 mg/kg for oral administration once daily for 7 days

Arm type	Experimental
Investigational medicinal product name	Nepadutant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Nepadutant oral solution 0.1 mg/kg for oral administration once daily for 7 days

Arm title	Nepadutant high dose

Arm description:

Nepadutant oral solution 0.5 mg/kg for oral administration once daily for 7 days

Arm type	Experimental
Investigational medicinal product name	Nepadutant oral solution 0.5 mg/kg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Nepadutant oral solution 0.5 mg/kg for oral administration once daily for 7 days

Arm title	Placebo

Arm description:

Placebo matching Nepadutant oral solution for oral administration once daily for 7 days

Arm type	Placebo

Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

once daily for 7 days

Number of subjects in period 1[1]	Nepadutant low dose	Nepadutant high dose	Placebo
Started	39	38	36
Completed	39	38	36

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: Two patients withdraw the consent: a total of 113 patients were considered in the ITT population and 114 for the safety population.
For the efficacy analysis 112 patients were considered, as one patient had no baseline recorded data.

Baseline characteristics

Reporting groups	
Reporting group title	Nepadutant low dose
Reporting group description:	
Nepadutant oral solution 0.1 mg/kg for oral administration once daily for 7 days	
Reporting group title	Nepadutant high dose
Reporting group description:	
Nepadutant oral solution 0.5 mg/kg for oral administration once daily for 7 days	
Reporting group title	Placebo
Reporting group description:	
Placebo matching Nepadutant oral solution for oral administration once daily for 7 days	

Reporting group values	Nepadutant low dose	Nepadutant high dose	Placebo
Number of subjects	39	38	36
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: weeks			
arithmetic mean	11.03	11.34	10.92
standard deviation	± 4.909	± 5.147	± 4.686
Gender categorical Units: Subjects			
Female	21	13	17
Male	18	25	19
not recorded	0	0	0

Reporting group values	Total		
Number of subjects	113		
Age categorical 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)	0		
Adolescents (12-17 years)	0		

Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: weeks			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	51		
Male	62		
not recorded	0		

End points

End points reporting groups

Reporting group title	Nepadutant low dose
Reporting group description:	
Nepadutant oral solution 0.1 mg/kg for oral administration once daily for 7 days	
Reporting group title	Nepadutant high dose
Reporting group description:	
Nepadutant oral solution 0.5 mg/kg for oral administration once daily for 7 days	
Reporting group title	Placebo
Reporting group description:	
Placebo matching Nepadutant oral solution for oral administration once daily for 7 days	

Primary: Absolute Change of the Mean Daily Crying and Fussing Time for Three Consecutive Days While on Treatment Versus Baseline.

End point title	Absolute Change of the Mean Daily Crying and Fussing Time for Three Consecutive Days While on Treatment Versus Baseline.
End point description:	
Efficacy assessment to be measured through "baby's day" diary recorded for three consecutive days while on treatment (i.e. starting from 6 pm on Day 4 and continued for 72 hours) vs baseline (i.e. starting from 6 pm on Day -4 until 1st treatment administration). Analysis population: 112 instead of 113, because 1 subject had no records at baseline and therefore the outcome could not be measured	
End point type	Primary
End point timeframe:	
Baseline and one week	

End point values	Nepadutant low dose	Nepadutant high dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	38	38	36	
Units: minute				
arithmetic mean (standard deviation)	-96.9 (± 75.12)	-119.2 (± 97.13)	-91.2 (± 76.2)	

Statistical analyses

Statistical analysis title	ANCOVA
Comparison groups	Nepadutant high dose v Placebo v Nepadutant low dose

Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.04
Method	ANCOVA

Secondary: Absolute Change in the Overall Parental Judgment After the First Dose of Treatment Versus Baseline

End point title	Absolute Change in the Overall Parental Judgment After the First Dose of Treatment Versus Baseline

End point description:

On a daily basis parents expressed an overall judgement on the study treatment effect based on a 6 rate categorical scale from 0 to 5 (where 0 is for "Not at all" and 5 is "Extremely".

The question was "How frustrating to you was your baby's crying today?"

End point type	Secondary

End point timeframe:

1 day

End point values	Nepadutant low dose	Nepadutant high dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	39	38	36	
Units: score range 0-5				
median (standard deviation)	-0.38 (± 0.771)	-068 (± 0.884)	-0.34 (± 0.596)	

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change in the Overall Parental Judgment at the End of Treatment Versus Baseline

End point title	Absolute Change in the Overall Parental Judgment at the End of Treatment Versus Baseline

End point description:

On a daily basis parents expressed an overall judgement on the study treatment effect based on a 6 rate categorical scale from 0 to 5 (where 0 is for "Not at all" and 5 is "Extremely".

The question was "How frustrating to you was your baby's crying today?"

End point type	Secondary

End point timeframe:

1 week

End point values	Nepadutant low dose	Nepadutant high dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	39	38	36	
Units: score 0-5				
median (standard deviation)	-1.24 (± 0.909)	-1.75 (± 1.186)	-1.23 (± 1.044)	

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change in the Overall Parental Judgment After Treatment Discontinuation Versus Baseline

End point title	Absolute Change in the Overall Parental Judgment After Treatment Discontinuation Versus Baseline

End point description:

On a daily basis parents expressed an overall judgement on the study treatment effect based on a 6 rate categorical scale from 0 to 5 (where 0 is for "Not at all" and 5 is "Extremely".

The question was "How frustrating to you was your baby's crying today?"

End point type	Secondary

End point timeframe:

10 days

End point values	Nepadutant low dose	Nepadutant high dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	39	38	36	
Units: score 0-5				
median (standard deviation)	-1.35 (± 0.857)	-1.78 (± 1.176)	-1.39 (± 0.896)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of 'Responder' Babies at the End of Treatment Period.

End point title	Percentage of 'Responder' Babies at the End of Treatment Period.

End point description:

Response is defined as a decrease of at least 50% of crying and fussing time during the last 3 days on treatment vs baseline.

Analysis population: 112 instead of 113, because 1 subject had no records at baseline and therefore the outcome could not be measured

End point type	Secondary

End point timeframe:
baseline and one week

End point values	Nepadutant low dose	Nepadutant high dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	38	38	36	
Units: patient	14	21	7	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: up to 4 weeks after the first drug intake	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	14.1
Reporting groups	
Reporting group title	Nepadutant low dose
Reporting group description: Nepadutant oral solution 0.1 mg/kg for oral administration once daily for 7 days	
Reporting group title	Nepadutant high dose
Reporting group description: Nepadutant oral solution 0.5 mg/kg for oral administration once daily for 7 days	
Reporting group title	Placebo
Reporting group description: Placebo matching Nepadutant oral solution for oral administration once daily for 7 days	

Serious adverse events	Nepadutant low dose	Nepadutant high dose	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 40 (0.00%)	1 / 38 (2.63%)	0 / 36 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Respiratory, thoracic and mediastinal disorders			
Bronchitis bacterial			
subjects affected / exposed	0 / 40 (0.00%)	1 / 38 (2.63%)	0 / 36 (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

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Nepadutant low dose	Nepadutant high dose	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 40 (22.50%)	7 / 38 (18.42%)	5 / 36 (13.89%)
Investigations			
Body temperature increased			

subjects affected / exposed	0 / 40 (0.00%)	1 / 38 (2.63%)	0 / 36 (0.00%)
occurrences (all)	0	1	0
Gamma-glutamyltransferase abnormal			
subjects affected / exposed	1 / 40 (2.50%)	0 / 38 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Crying			
subjects affected / exposed	0 / 40 (0.00%)	0 / 38 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 40 (2.50%)	0 / 38 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 40 (0.00%)	1 / 38 (2.63%)	0 / 36 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 40 (0.00%)	0 / 38 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Frequent bowel movements			
subjects affected / exposed	1 / 40 (2.50%)	0 / 38 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Infrequent bowel movements			
subjects affected / exposed	1 / 40 (2.50%)	0 / 38 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Regurgitation			
subjects affected / exposed	1 / 40 (2.50%)	0 / 38 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	1 / 40 (2.50%)	0 / 38 (0.00%)	1 / 36 (2.78%)
occurrences (all)	1	0	1
Salivary hypersecretion			
subjects affected / exposed	0 / 40 (0.00%)	1 / 38 (2.63%)	0 / 36 (0.00%)
occurrences (all)	0	1	0

Aphthous ulcer			
subjects affected / exposed	1 / 40 (2.50%)	0 / 38 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 40 (0.00%)	0 / 38 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Apnoea			
subjects affected / exposed	1 / 40 (2.50%)	0 / 38 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 40 (2.50%)	0 / 38 (0.00%)	1 / 36 (2.78%)
occurrences (all)	1	0	1
Skin lesion			
subjects affected / exposed	0 / 40 (0.00%)	1 / 38 (2.63%)	0 / 36 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 April 2011	Harmonisation of the slightly different protocol versions which are in force in three participating Countries as consequence of the country specific Amendments implemented in response to Regulatory Authorities (RAs), Ethical Committees (ECs) and Institutional Review Boards. Enlargement of the inclusion to infants who are fed with mixed milk or formula milk, provided that the following specifications on infant's dietary regimen are met: a) stable and well tolerated dietary regimen b) no change in the dietary regimen until the end of the 7 day treatment period c) cow milk allergy must be excluded d) complementary food not allowed • Deletion of faecal analysis which was intended to be performed as sub-study in Finnish sites, no longer participating to the study. • Update on the Project Responsible Person appointed by the CRO.
21 December 2011	Main changes: The age range of eligible patients has been extended by increasing the age upper limit to < 20 weeks at screening visit. The allowed PCA (post-conceptual age) at screening visit has been decreased from >44 to >40 weeks. • Revision of the inclusion criteria specifically pertaining the diagnosis of colic has been made so that a total of 6 hours crying and/or fussing time over a three days screening period is now considered adequate to reflect the Wessel criteria based on a weekly observation time ("paroxysm of irritability, fussing or crying that start and stop without obvious cause for >3h/day, >3 days/week for at least one week"). • Study procedures have been reviewed to avoid unnecessary restriction and therefore to facilitate the inclusion of patients. In particular: - the start of the wash-out period for the exclusion of any pharmacological treatment has been shortened to 24 h before starting the "baby's day" diary recording at screening (i.e. the day before Day -4) instead of 1 week prior randomisation. As the minimum screening period is 4 days, the wash-out period was at least of 5 days before starting the study treatment. - no change in probiotics and herbal tea intake is required, from 24 h before starting recording the "baby's day" diary up to completion of post treatment period. • to remove the PK sampling scheduled at visit 3 in order to further reduce any patient discomfort. The "baby's day" diary has been simplified Administrative changes: number of sites, CRO name,

29 October 2012	New sites in Asia and Australia have been included and ClinActis Ltd is the CRO in charge to manage the Asian and Australian sites. The contact details of the CRO have been added to the protocol. • The "Study Responsibility" section has been updated. • Exclusion criterion 5 clarifies that the daily infant's habits should not be changed during the study conduct, including the use of probiotics, herbal tea and other home remedy. • Paper CRF was replaced by electronic CRF. • Other minor rewording and typos have been included in the protocol review

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported