Clinical trial results:
Equimolar Mixture of Oxygen and Nitrous Oxide (EMONO) for the Treatment of Peripheral Neuropathic Pain: a Randomised, International, Multicentre, Placebo-Controlled, Phenotype-stratified Phase IIa Study

Summary

EudraCT number	2015-004779-64
Trial protocol	DE FR
Global end of trial date	30 August 2018

Results information

Result version number	v1 (current)
This version publication date	14 November 2019
First version publication date	14 November 2019

Trial information

Trial identification

Sponsor protocol code	ALMED-15-C2-054

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02957851
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Air Liquide Santé International
Sponsor organisation address	75, quai d'Orsay, Paris, France, 75007
Public contact	Healthcare Communication & Public Affairs Director, Air Liquide Santé International, muriel.doucet@airliquide.com
Scientific contact	Clinical Development Physician, Air Liquide Santé International, fralsi-ctpublication@airliquide.com

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	23 October 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 August 2018
Global end of trial reached?	Yes
Global end of trial date	30 August 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effect of 3 consecutive days of one-hour administration of Nitrous Oxide/Oxygen 50%/50% (EMONO) versus placebo as Oxygen/Nitrogen 22%/78% (synthetic medical air), in add-on therapy to chronic analgesic treatments, on average pain intensity in patients with chronic peripheral neuropathic pain.

Protection of trial subjects:

The study was conducted in compliance with Good Clinical Practice (GCP) guidelines, and in keeping with the most recent revised version of the Declaration of Helsinki and in the European Directive 2001/20/CE on 4th April 2001 on the approximation of the laws, regulations and administrative provisions of the member states relating to the implementation of GCP in the conduct of the clinical trials on medicinal products for human use.
The Protocol and Substantial Amendments were submitted to the Independent Ethics Committee (IEC) and national Competent Authority (CA) for approval in each participating country.
The enrolment of the patients in the study started only after the written approvals of the corresponding IEC and national CA.

Background therapy:

Drugs with anti-NMDA mechanism of action such as ketamine were not allowed during the study and within the 4 weeks before the Selection visit (V0).

All treatments for chronic neuropathic pain and non drugs therapies such as hypnosis being currently used by the patients at the entry into the study were allowed throughout the study providing these treatments were stable since at least 4 weeks prior the Selection visit V0.

Other concomitant treatments prescribed for co-morbidities (hypertension, dyslipidemia...) or associated chronic diseases (such as diabetes, cardiovascular disease, respiratory diseases...) were allowed.

Rescue therapy limited to paracetamol was authorised in case the pain intensity increased too much according to the patient during the study.

Evidence for comparator:

The comparator is a placebo, here synthetic medical air (Oxygen/Nitrogen 22%/78%).

Actual start date of recruitment	21 November 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 270
Country: Number of subjects enrolled	Germany: 17
Worldwide total number of subjects	287
EEA total number of subjects	287

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	213
From 65 to 84 years	72
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

A total of 287 patients were enrolled (240 met the inclusion criteria) from 22 centres in 2 countries; 2 in Germany and 20 in France
First Patient Enrolled: 21 November 2016
Last Patient Completed: 30 August 2018

Pre-assignment

Screening details:

Adult patients with chronic peripheral neuropathic pain. Diagnosis based on DN4 questionnaire (score ≥ 4) and NeuPSIG criteria ("definite" or "probable" levels). Baseline pain intensity between 4 and 9 on NRS. Analgesic medications had to be stable since at least 4 weeks prior to the study.

Pre-assignment period milestones

Number of subjects started	287
Number of subjects completed	240

Pre-assignment subject non-completion reasons

Reason: Number of subjects	At least one selection/inclusion criterion not met: 39
Reason: Number of subjects	Consent withdrawn by subject: 5
Reason: Number of subjects	Adverse event, non-fatal: 1
Reason: Number of subjects	Protocol deviation: 1
Reason: Number of subjects	Subject not available: 1

Period 1

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

Blinding implementation details:

Patient and the physician (Investigator 1) who performed selection, inclusion, stratification and follow-ups visits (including study end) remained blinded as to the nature of study treatment. Only caregiver (Investigator 2) who performed randomisation according to stratification and administered the treatment was unblinded. All information regarding randomisation and administration have been collected in a separate source document.

Arms

Are arms mutually exclusive?	Yes
Arm title	EMONO

Arm description:

Equimolar gases mixture of medicinal nitrous oxide 50% and medicinal oxygen 50% (EMONO) from Air Liquide Santé International.

Arm type	Experimental
Investigational medicinal product name	EMONO
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Medicinal gas, compressed
Routes of administration	Inhalation use

Dosage and administration details:

60 min per day during 3 consecutive days.

Arm title	Placebo

Arm description:

Oxygen/Nitrogen 22%/78% (synthetic medical air)

Arm type	Placebo
Investigational medicinal product name	Medical Air
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Medicinal gas, compressed
Routes of administration	Inhalation use

Dosage and administration details:

60 min per day during 3 consecutive days.

Number of subjects in period 1[1]	EMONO	Placebo
Started	120	120
Completed	112	117
Not completed	8	3
Subject decided not to participate anymore	1	-
Consent withdrawn by subject	3	1
Adverse event, non-fatal	1	-
Subject decision	1	-
Subject non available	-	1
Unavailability of the subject	1	-
Subject could not come on site (personal reason)	-	1
Lost to follow-up	1	-

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: 287 subjects signed an informed consent. 240 subjects received at least one administration of investigational medicinal product.

Baseline characteristics

Reporting groups	
Reporting group title	EMONO
Reporting group description:	
Equimolar gases mixture of medicinal nitrous oxide 50% and medicinal oxygen 50% (EMONO) from Air Liquide Santé International.	
Reporting group title	Placebo
Reporting group description:	
Oxygen/Nitrogen 22%/78% (synthetic medical air)	

Reporting group values	EMONO	Placebo	Total
Number of subjects	120	120	240
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	51.8	54.4	
standard deviation	± 14.8	± 14.5	-
Gender categorical			
Units: Subjects			
Female	64	67	131
Male	56	53	109
Peripheral neuropathy aetiology			
Units: Subjects			
Post-traumatic or post-surgical nerve injury	73	76	149
Polyneuropathy including diabetic neuropathy	32	33	65
Post-herpetic neuralgia	14	9	23
Other	1	2	3
NPSI Evoked/non Evoked Pain Repartition			
Presence or absence of evoked pain as assessed by the Neuropathic Pain Symptom Inventory (NPSI).			
Units: Subjects			
Subjects with evoked pain	103	108	211
Subjects without evoked pain	17	12	29
At least one past or current chronic neuropathic pain treatment			
Units: Subjects			
Yes	118	120	238
No	2	0	2
At least one past neuropathic pain treatment failure			
Units: Subjects			
Yes	101	108	209
No	19	12	31
At least one chronic neuropathic pain treatment at baseline			
Units: Subjects			

Yes	93	91	184
No	27	29	56
At least one anti-epileptic for neuropathic pain ongoing at baseline Units: Subjects			
Yes	38	47	85
No	82	73	155
At least one antidepressant for neuropathic pain ongoing at baseline Units: Subjects			
Yes	43	45	88
No	77	75	152
At least one opioid and derivates for neuropathic pain ongoing at baseline Units: Subjects			
Yes	48	50	98
No	72	70	142
At least one local neuropathic pain treatment ongoing at baseline Units: Subjects			
Yes	30	21	51
No	90	99	189
At least one other non-drug therapy for neuropathic pain ongoing at baseline Units: Subjects			
Yes	5	5	10
No	115	115	230
Number of chronic neuropathic pain treatments at baseline Units: Subjects			
<2	67	62	129
≥2	53	58	111
HADS-Anxiety Units: Subjects			
Normal (Score 0-7)	63	51	114
Mild (Score 8-10)	24	32	56
Moderate (Score 11-14)	18	31	49
Severe (Score 15-21)	12	4	16
Missing	3	2	5
HADS-Depression Units: Subjects			
Normal (Score 0-7)	62	63	125
Mild (Score 8-10)	30	28	58
Moderate (Score 11-14)	17	22	39
Severe (Score 15-21)	9	5	14
Missing	2	2	4
At least one on demand/rescue therapy			
On Demand and/or rescue therapies were reported in the booklets by the patients. Timeframe: during the 7-day baseline period.			
Units: Subjects			
Yes	55	61	116
No	65	59	124
At least one on demand/rescue therapy (only opioid treatments)			

On Demand and/or rescue therapies were reported in the booklets by the patients. Timeframe: during the 7-day baseline period.			
Units: Subjects			
Yes	21	33	54
No	99	87	186
Disease duration			
Units: months			
arithmetic mean	52	55	
standard deviation	± 48	± 34	-
Number of Trts with Past Therapeutic Failure			
Number of treatments (Trts) calculated in patients with at least one past neuropathic pain treatment failure.			
Units: treatments per subject			
arithmetic mean	4.4	4.3	
standard deviation	± 3.1	± 2.9	-
Mean 7-day NRS at baseline			
Mean NRS calculated from daily NRS assessments collected from a period of 7 days before randomisation (7-day baseline period).			
Units: units on a scale			
arithmetic mean	6.42	6.41	
standard deviation	± 1.25	± 1.08	-
NPSI total score			
Units: units on a scale			
arithmetic mean	47.4	46.0	
standard deviation	± 17.8	± 16.6	-
NPSI evoked pain score			
Units: units on a scale			
arithmetic mean	4.78	4.79	
standard deviation	± 2.32	± 2.38	-
SF-12 Mental Component Summary			
Units: units on a scale			
arithmetic mean	41.6	42.4	
standard deviation	± 10.5	± 9.1	-
SF-12 Physical Component Summary			
Units: units on a scale			
arithmetic mean	37.1	35.9	
standard deviation	± 8.5	± 8.1	-
SF-12 Bodily pain			
Units: units on a scale			
arithmetic mean	33.8	33.2	
standard deviation	± 8.8	± 8.0	-

Subject analysis sets

Subject analysis set title	EMONO - mFAS
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Randomised patients who received three administrations of EMONO (with at least one complete administration) and had at least 4 evaluations of NRS in the first week post-treatment. A complete administration was defined as an administration with an exposure between 55 and 65 minutes with no more than 5 minutes without treatment administration.
The mFAS was used for efficacy analyses.

Subject analysis set title	Placebo - mFAS

Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Randomised patients who received three administrations of Placebo (with at least one complete administration) and had at least 4 evaluations of NRS in the first week post-treatment. A complete administration was defined as an administration with an exposure between 55 and 65 minutes with no more than 5 minutes without treatment administration.
The mFAS was used for efficacy analyses.

Reporting group values	EMONO - mFAS	Placebo - mFAS	
Number of subjects	103	118	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	52.4	54.6	
standard deviation	± 14.6	± 14.6	
Gender categorical Units: Subjects			
Female	54	66	
Male	49	52	
Peripheral neuropathy aetiology Units: Subjects			
Post-traumatic or post-surgical nerve injury	61	74	
Polyneuropathy including diabetic neuropathy	28	33	
Post-herpetic neuralgia	13	9	
Other	1	2	
NPSI Evoked/non Evoked Pain Repartition			
Presence or absence of evoked pain as assessed by the Neuropathic Pain Symptom Inventory (NPSI).			
Units: Subjects			
Subjects with evoked pain	91	106	
Subjects without evoked pain	12	12	
At least one past or current chronic neuropathic pain treatment Units: Subjects			
Yes	102	118	
No	1	0	
At least one past neuropathic pain treatment failure Units: Subjects			
Yes	89	106	
No	14	12	
At least one chronic neuropathic pain treatment at baseline Units: Subjects			
Yes	82	90	
No	21	28	
At least one anti-epileptic for neuropathic pain ongoing at baseline Units: Subjects			
Yes	32	46	

No	88	74	
At least one antidepressant for neuropathic pain ongoing at baseline Units: Subjects			
Yes	38	44	
No	65	74	
At least one opioid and derivates for neuropathic pain ongoing at baseline Units: Subjects			
Yes	43	49	
No	60	69	
At least one local neuropathic pain treatment ongoing at baseline Units: Subjects			
Yes	25	21	
No	78	97	
At least one other non-drug therapy for neuropathic pain ongoing at baseline Units: Subjects			
Yes	4	5	
No	99	113	
Number of chronic neuropathic pain treatments at baseline Units: Subjects			
<2	57	61	
≥2	46	57	
HADS-Anxiety Units: Subjects			
Normal (Score 0-7)	54	51	
Mild (Score 8-10)	20	31	
Moderate (Score 11-14)	18	30	
Severe (Score 15-21)	9	4	
Missing	2	2	
HADS-Depression Units: Subjects			
Normal (Score 0-7)	52	62	
Mild (Score 8-10)	26	28	
Moderate (Score 11-14)	15	21	
Severe (Score 15-21)	9	5	
Missing	1	2	
At least one on demand/rescue therapy			
On Demand and/or rescue therapies were reported in the booklets by the patients. Timeframe: during the 7-day baseline period.			
Units: Subjects			
Yes	46	60	
No	57	58	
At least one on demand/rescue therapy (only opioid treatments)			
On Demand and/or rescue therapies were reported in the booklets by the patients. Timeframe: during the 7-day baseline period.			
Units: Subjects			
Yes	21	32	
No	82	86	

Disease duration Units: months arithmetic mean standard deviation	 54 ± 50	 55 ± 34	
Number of Trts with Past Therapeutic Failure			
Number of treatments (Trts) calculated in patients with at least one past neuropathic pain treatment failure.			
Units: treatments per subject arithmetic mean standard deviation	 4.4 ± 2.7	 4.2 ± 2.8	
Mean 7-day NRS at baseline			
Mean NRS calculated from daily NRS assessments collected from a period of 7 days before randomisation (7-day baseline period).			
Units: units on a scale arithmetic mean standard deviation	 6.42 ± 1.27	 6.43 ± 1.07	
NPSI total score Units: units on a scale arithmetic mean standard deviation	 47.2 ± 17.5	 46.0 ± 16.6	
NPSI evoked pain score Units: units on a scale arithmetic mean standard deviation	 4.92 ± 2.25	 4.80 ± 2.39	
SF-12 Mental Component Summary Units: units on a scale arithmetic mean standard deviation	 41.5 ± 10.3	 42.5 ± 9.2	
SF-12 Physical Component Summary Units: units on a scale arithmetic mean standard deviation	 36.9 ± 8.5	 35.9 ± 8.1	
SF-12 Bodily pain Units: units on a scale arithmetic mean standard deviation	 33.2 ± 8.3	 33.3 ± 8.0	

End points

End points reporting groups

Reporting group title	EMONO

Reporting group description:

Equimolar gases mixture of medicinal nitrous oxide 50% and medicinal oxygen 50% (EMONO) from Air Liquide Santé International.

Reporting group title	Placebo

Reporting group description:

Oxygen/Nitrogen 22%/78% (synthetic medical air)

Subject analysis set title	EMONO - mFAS
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Randomised patients who received three administrations of EMONO (with at least one complete administration) and had at least 4 evaluations of NRS in the first week post-treatment. A complete administration was defined as an administration with an exposure between 55 and 65 minutes with no more than 5 minutes without treatment administration.
The mFAS was used for efficacy analyses.

Subject analysis set title	Placebo - mFAS
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Randomised patients who received three administrations of Placebo (with at least one complete administration) and had at least 4 evaluations of NRS in the first week post-treatment. A complete administration was defined as an administration with an exposure between 55 and 65 minutes with no more than 5 minutes without treatment administration.
The mFAS was used for efficacy analyses.

Primary: Change in mean pain intensity (assessed by NRS)

End point title	Change in mean pain intensity (assessed by NRS)

End point description:

Change was calculated between the mean of the daily NRS records from the first week after last treatment administration and the mean of the daily NRS records from the 7-day baseline period.

End point type	Primary

End point timeframe:

Between the 7-day baseline period and the first 7-day after the last administration of treatment.

End point values	EMONO - mFAS	Placebo - mFAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	103	118		
Units: units on a scale				
arithmetic mean (standard deviation)	-1.02 (± 1.50)	-0.81 (± 1.30)		

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

ANCOVA with mean 7-day baseline pain intensity score, sensory phenotype at baseline (presence or absence of evoked pain) and treatment group as factors.

Comparison groups	EMONO - mFAS v Placebo - mFAS
Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2465
Method	ANCOVA
Parameter estimate	LS-mean difference
Point estimate	-0.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.59
upper limit	0.15

Secondary: Weekly Change in mean pain intensity (assessed by NRS) up to 28 days

End point title	Weekly Change in mean pain intensity (assessed by NRS) up to 28 days

End point description:

Weekly pain intensity scores were calculated as the mean of the daily NRS records for each week. Changes were calculated from the 7-day baseline period.

End point type	Secondary

End point timeframe:

Between the 7-day baseline period and each week after the last administration of treatment up to 28 days.

End point values	EMONO - mFAS	Placebo - mFAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	103[1]	118[2]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Week 1	-1.02 (± 1.50)	-0.81 (± 1.30)		
Week 2	-0.93 (± 1.56)	-0.68 (± 1.35)		
Week 3	-0.90 (± 1.53)	-0.67 (± 1.45)		
Week 4	-0.83 (± 1.41)	-0.67 (± 1.47)		

Notes:

[1] - mFAS: 3 administrations with at least one complete
Week 1=103; Week 2=101; Week 3=100; Week 4=99

[2] - mFAS: 3 administrations with at least one complete
Week 1=118; Week 2=117; Week 3=117; Week 4=116

Statistical analyses

Statistical analysis title	ANCOVA Week 1 - mFAS

Statistical analysis description:

ANCOVA comparing EMONO and Placebo at Week 1 in the mFAS, with mean 7-day baseline pain intensity score, sensory phenotype at baseline (presence or absence of evoked pain) and treatment group as factors.

Comparison groups	EMONO - mFAS v Placebo - mFAS

Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2465
Method	ANCOVA
Parameter estimate	LS-mean difference
Point estimate	-0.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.59
upper limit	0.15

Statistical analysis title	ANCOVA Week 2 - mFAS

Statistical analysis description:

ANCOVA comparing EMONO and Placebo at Week 2 in the mFAS, with mean 7-day baseline pain intensity score, sensory phenotype at baseline (presence or absence of evoked pain) and treatment group as factors.
Number of subjects included in analysis = 218

Comparison groups	EMONO - mFAS v Placebo - mFAS
Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2227
Method	ANCOVA
Parameter estimate	LS-mean difference
Point estimate	-0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.63
upper limit	0.15

Statistical analysis title	ANCOVA Week 3 - mFAS

Statistical analysis description:

ANCOVA comparing EMONO and Placebo at Week 3 in the mFAS, with mean 7-day baseline pain intensity score, sensory phenotype at baseline (presence or absence of evoked pain) and treatment group as factors.
Number of subjects included in analysis = 217

Comparison groups	EMONO - mFAS v Placebo - mFAS
Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2624
Method	ANCOVA
Parameter estimate	LS-mean difference
Point estimate	-0.23

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.63
upper limit	0.17

Statistical analysis title	ANCOVA Week 4 - mFAS

Statistical analysis description:

ANCOVA comparing EMONO and Placebo at Week 4 in the mFAS, with mean 7-day baseline pain intensity score, sensory phenotype at baseline (presence or absence of evoked pain) and treatment group as factors.
Number of subjects included in analysis = 215

Comparison groups	EMONO - mFAS v Placebo - mFAS
Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3949
Method	ANCOVA
Parameter estimate	LS-mean difference
Point estimate	-0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.56
upper limit	0.22

Secondary: Proportion of subjects with 30% reduction in pain intensity (assessed by NRS) up to 28 days

End point title	Proportion of subjects with 30% reduction in pain intensity (assessed by NRS) up to 28 days

End point description:

Weekly pain intensity scores were calculated as the mean of the pain intensity score records for each week.
A patient was considered as a responder to a 30% reduction of pain intensity score at a given week if there was a decrease in the weekly mean NRS score equal or greater than 30%

End point type	Secondary

End point timeframe:

Between the 7-day baseline period and each week after the last administration of treatment up to 28 days.

End point values	EMONO - mFAS	Placebo - mFAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	103[3]	118[4]		
Units: subjects				
Week 1	28	23		
Week 2	26	20		
Week 3	30	19		
Week 4	25	23		

Notes:

[3] - mFAS: 3 administrations with at least one complete
Week 1=103; Week 2=101; Week 3=100; Week 4=99

[4] - mFAS: 3 administrations with at least one complete
Week 1=118; Week 2=117; Week 3=117; Week 4=116

Statistical analyses

Statistical analysis title	Chi-Square test - Week 1
Comparison groups	EMONO - mFAS v Placebo - mFAS
Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1757
Method	Chi-squared

Statistical analysis title	Chi-Square test - Week 2
Statistical analysis description:	
Number of subjects included in analysis = 218	
Comparison groups	EMONO - mFAS v Placebo - mFAS
Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1186
Method	Chi-squared

Statistical analysis title	Chi-Square test - Week 3
Statistical analysis description:	
Number of subjects included in analysis = 217	
Comparison groups	EMONO - mFAS v Placebo - mFAS
Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0157
Method	Chi-squared

Statistical analysis title	Chi-Square test - Week 4
Statistical analysis description: Number of subjects included in analysis = 215	
Comparison groups	EMONO - mFAS v Placebo - mFAS
Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.341
Method	Chi-squared

Secondary: Weekly Evolution of NPSI Total Score up to 28 days

End point title	Weekly Evolution of NPSI Total Score up to 28 days
End point description: Evolution assessed using percent change score from baseline.	
End point type	Secondary
End point timeframe: Between baseline and the end of each week after the last administration of treatment (Day 10, Day 17, Day 24, Day 31).	

End point values	EMONO - mFAS	Placebo - mFAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	103[5]	118[6]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Day 10	-20.8 (± 32.0)	-17.1 (± 38.6)		
Day 17	-22.1 (± 28.6)	-14.8 (± 31.3)		
Day 24	-17.9 (± 31.7)	-9.9 (± 36.2)		
Day 31	-17.6 (± 36.4)	-12.0 (± 37.7)		

Notes:

[5] - mFAS: 3 administrations with at least one complete
Day 10=90; Day 17=92; Day 24=93; Day 31=89

[6] - mFAS: 3 administrations with at least one complete
Day 10=104; Day 17=108; Day 24=106; Day 31=106

Statistical analyses

Statistical analysis title	ANCOVA Day 10 - mFAS
Statistical analysis description: ANCOVA comparing EMONO and Placebo at Day 10 in the mFAS, with baseline score, sensory phenotype at baseline (presence or absence of evoked pain) and treatment group as factors. Number of subjects included in analysis = 194	
Comparison groups	EMONO - mFAS v Placebo - mFAS

Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4149
Method	ANCOVA
Parameter estimate	LS-mean difference
Point estimate	-4.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.24
upper limit	5.9

Statistical analysis title	ANCOVA Day 17 - mFAS

Statistical analysis description:

ANCOVA comparing EMONO and Placebo at Day 17 in the mFAS, with baseline score, sensory phenotype at baseline (presence or absence of evoked pain) and treatment group as factors.
Number of subjects included in analysis = 200

Comparison groups	EMONO - mFAS v Placebo - mFAS
Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0795
Method	ANCOVA
Parameter estimate	LS-mean difference
Point estimate	-7.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.99
upper limit	0.9

Statistical analysis title	ANCOVA Day 24 - mFAS

Statistical analysis description:

ANCOVA comparing EMONO and Placebo at Day 24 in the mFAS, with baseline score, sensory phenotype at baseline (presence or absence of evoked pain) and treatment group as factors.
Number of subjects included in analysis = 199

Comparison groups	EMONO - mFAS v Placebo - mFAS
Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0985
Method	ANCOVA
Parameter estimate	LS-mean difference
Point estimate	-8.06

Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.64
upper limit	1.52

Statistical analysis title	ANCOVA Day 31 - mFAS

Statistical analysis description:

ANCOVA comparing EMONO and Placebo at Day 31 in the mFAS, with baseline score, sensory phenotype at baseline (presence or absence of evoked pain) and treatment group as factors.
Number of subjects included in analysis = 195

Comparison groups	EMONO - mFAS v Placebo - mFAS
Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2808
Method	ANCOVA
Parameter estimate	LS-mean difference
Point estimate	-5.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.37
upper limit	4.78

Secondary: Weekly Evolution of NPSI Evoked Pain Score up to 28 days

End point title	Weekly Evolution of NPSI Evoked Pain Score up to 28 days

End point description:

Evolution assessed using percent change score from baseline. For patients with a baseline score of 0, no percent change was calculable.

End point type	Secondary

End point timeframe:

Between baseline and the end of each week after the last administration of treatment (Day 10, Day 17, Day 24, Day 31).

End point values	EMONO - mFAS	Placebo - mFAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	103[7]	118[8]		
Units: units on a scale				
arithmetic mean (standard deviation)				
Day 10	-24.9 (± 44.4)	-19.8 (± 41.3)		
Day 17	-23.3 (± 42.0)	-12.9 (± 48.0)		
Day 24	-23.3 (± 42.6)	-7.4 (± 58.9)		
Day 31	-22.5 (± 44.2)	-13.1 (± 43.8)		

Notes:

[7] - mFAS: 3 administrations with at least one complete
Day 10=93; Day 17=95; Day 24=95; Day 31=92
[8] - mFAS: 3 administrations with at least one complete
Day 10=103; Day 17=111; Day 24=112; Day 31=107

Statistical analyses

Statistical analysis title	ANCOVA Day 10 - mFAS

Statistical analysis description:

ANCOVA comparing EMONO and Placebo at Day 10 in the mFAS, with baseline score, sensory phenotype at baseline (presence or absence of evoked pain) and treatment group as factors.
Number of subjects included in analysis = 196

Comparison groups	EMONO - mFAS v Placebo - mFAS
Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3236
Method	ANCOVA
Parameter estimate	LS-mean difference
Point estimate	-6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.95
upper limit	5.96

Statistical analysis title	ANCOVA Day 17 - mFAS

Statistical analysis description:

ANCOVA comparing EMONO and Placebo at Day 17 in the mFAS, with baseline score, sensory phenotype at baseline (presence or absence of evoked pain) and treatment group as factors.
Number of subjects included in analysis = 206

Comparison groups	EMONO - mFAS v Placebo - mFAS
Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.045
Method	ANCOVA
Parameter estimate	LS-mean difference
Point estimate	-12.24

Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.21
upper limit	-0.28

Statistical analysis title	ANCOVA Day 24 - mFAS

Statistical analysis description:

ANCOVA comparing EMONO and Placebo at Day 24 in the mFAS, with baseline score, sensory phenotype at baseline (presence or absence of evoked pain) and treatment group as factors.
Number of subjects included in analysis = 207

Comparison groups	EMONO - mFAS v Placebo - mFAS
Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0124
Method	ANCOVA
Parameter estimate	LS-mean difference
Point estimate	-17.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	-31.5
upper limit	-3.87

Statistical analysis title	ANCOVA Day 31 - mFAS

Statistical analysis description:

ANCOVA comparing EMONO and Placebo at Day 31 in the mFAS, with baseline score, sensory phenotype at baseline (presence or absence of evoked pain) and treatment group as factors.
Number of subjects included in analysis = 199

Comparison groups	EMONO - mFAS v Placebo - mFAS
Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0802
Method	ANCOVA
Parameter estimate	LS-mean difference
Point estimate	-10.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23
upper limit	1.32

Secondary: Evolution of Quality of Life, assessed by SF-12

End point title	Evolution of Quality of Life, assessed by SF-12

End point description:

Evolution assessed using change from baseline in SF-12 Mental Component Summary, SF-12 Physical Component Summary and SF-12 bodily-pain.
SF-12v2® Health Survey was used for the study. Scoring was performed using the QualityMetric Health OutcomesTM Scoring Software 4.5.

End point type	Secondary

End point timeframe:

Between baseline and 28 days after last treatment administration (study end).

End point values	EMONO - mFAS	Placebo - mFAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	97	114		
Units: units on a scale				
arithmetic mean (standard deviation)				
Mental Component Summary (MCS)	2.01 (± 7.64)	1.30 (± 7.79)		
Physical Component Summary (PCS)	0.26 (± 6.15)	-0.13 (± 6.60)		
Bodily pain	3.35 (± 8.27)	1.19 (± 7.35)		

Statistical analyses

Statistical analysis title	ANCOVA MCS - mFAS

Statistical analysis description:

ANCOVA comparing EMONO and Placebo MCS change from baseline in the mFAS, with baseline score, sensory phenotype at baseline (presence or absence of evoked pain) and treatment group as factors.

Comparison groups	EMONO - mFAS v Placebo - mFAS
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7181
Method	ANCOVA
Parameter estimate	LS-mean difference
Point estimate	0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.57
upper limit	2.28

Statistical analysis title	ANCOVA PCS - mFAS

Statistical analysis description:

ANCOVA comparing EMONO and Placebo PCS change from baseline in the mFAS, with baseline score,

sensory phenotype at baseline (presence or absence of evoked pain) and treatment group as factors.

Comparison groups	EMONO - mFAS v Placebo - mFAS
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3848
Method	ANCOVA
Parameter estimate	LS-mean difference
Point estimate	0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.91
upper limit	2.35

Statistical analysis title	ANCOVA Bodily pain - mFAS

Statistical analysis description:

ANCOVA comparing EMONO and Placebo bodily pain change from baseline in the mFAS, with baseline score, sensory phenotype at baseline (presence or absence of evoked pain) and treatment group as factors.

Comparison groups	EMONO - mFAS v Placebo - mFAS
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0346
Method	ANCOVA
Parameter estimate	LS-mean difference
Point estimate	2.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.15
upper limit	4.06

Secondary: Proportion of subjects PGIC responders

End point title	Proportion of subjects PGIC responders

End point description:

A patient was considered as a responder in PGIC if the patient improved, i.e. answered one of the following item: minimally improved, much improved or very much improved.

End point type	Secondary

End point timeframe:

At the end of each week after the last administration of treatment (Day 10, Day 17, Day 24, Day 31).

End point values	EMONO - mFAS	Placebo - mFAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	103[9]	118[10]		
Units: subjects				
Day 10	45	37		
Day 17	50	34		
Day 24	44	35		
Day 31	44	37		

Notes:

[9] - mFAS: 3 administrations with at least one complete
Day 10=102; Day 17=96; Day 24=94; Day 31=93

[10] - mFAS: 3 administrations with at least one complete
Day 10=115; Day 17=113; Day 24=113; Day 31=112

Statistical analyses

Statistical analysis title	Chi-Square test - Day 10
Statistical analysis description:	
Number of subjects included in analysis = 217	
Comparison groups	EMONO - mFAS v Placebo - mFAS
Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0701
Method	Chi-squared

Statistical analysis title	Chi-Square test - Day 17
Statistical analysis description:	
Number of subjects included in analysis = 209	
Comparison groups	EMONO - mFAS v Placebo - mFAS
Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0012
Method	Chi-squared

Statistical analysis title	Chi-Square test - Day 24
Statistical analysis description:	
Number of subjects included in analysis = 207	
Comparison groups	EMONO - mFAS v Placebo - mFAS
Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0195
Method	Chi-squared

Statistical analysis title	Chi-Square test - Day 31
Statistical analysis description:	
Number of subjects included in analysis = 205	
Comparison groups	EMONO - mFAS v Placebo - mFAS
Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0374
Method	Chi-squared

Secondary: Weekly Evolution of HADS-Anxiety up to 28 days	
End point title	Weekly Evolution of HADS-Anxiety up to 28 days
End point description:	
At each timepoint, the HADS-Anxiety score was categorised as Normal (Score 0-7), Mild (Score 8-10), Moderate (Score 11-14) or Severe (Score 15-21).	
End point type	Secondary
End point timeframe:	
At the end of each week after the last administration of treatment (Day 10, Day 17, Day 24, Day 31).	

End point values	EMONO - mFAS	Placebo - mFAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	103	118		
Units: subjects				
Day 10 - Normal (score 0-7)	56	59		
Day 10 - Mild (score 8-10)	19	31		
Day 10 - Moderate (score 11-14)	20	19		
Day 10 - Severe (score 15-21)	5	5		
Day 17 - Normal (score 0-7)	60	67		
Day 17 - Mild (score 8-10)	17	22		
Day 17 - Moderate (score 11-14)	11	19		
Day 17 - Severe (score 15-21)	6	5		
Day 24 - Normal (score 0-7)	59	67		
Day 24 - Mild (score 8-10)	16	23		
Day 24 - Moderate (score 11-14)	15	15		
Day 24 - Severe (score 15-21)	6	7		
Day 31 - Normal (score 0-7)	56	62		
Day 31 - Mild (score 8-10)	18	28		
Day 31 - Moderate (score 11-14)	17	14		
Day 31 - Severe (score 15-21)	3	8		

Statistical analyses

No statistical analyses for this end point

Secondary: Weekly Evolution of HADS-Depression up to 28 days

End point title	Weekly Evolution of HADS-Depression up to 28 days

End point description:

At each timepoint, the HADS-Depression score was categorised as Normal (Score 0-7), Mild (Score 8-10), Moderate (Score 11-14) or Severe (Score 15-21).

End point type	Secondary

End point timeframe:

At the end of each week after the last administration of treatment (Day 10, Day 17, Day 24, Day 31).

End point values	EMONO - mFAS	Placebo - mFAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	103	118		
Units: subjects				
Day 10 - Normal (score 0-7)	51	59		
Day 10 - Mild (score 8-10)	23	33		
Day 10 - Moderate (score 11-14)	18	20		
Day 10 - Severe (score 15-21)	8	2		
Day 17 - Normal (score 0-7)	52	60		
Day 17 - Mild (score 8-10)	21	30		
Day 17 - Moderate (score 11-14)	17	22		
Day 17 - Severe (score 15-21)	4	3		
Day 24 - Normal (score 0-7)	52	56		
Day 24 - Mild (score 8-10)	24	34		
Day 24 - Moderate (score 11-14)	15	20		
Day 24 - Severe (score 15-21)	5	3		
Day 31 - Normal (score 0-7)	49	55		
Day 31 - Mild (score 8-10)	25	30		
Day 31 - Moderate (score 11-14)	13	25		
Day 31 - Severe (score 15-21)	7	2		

Statistical analyses

No statistical analyses for this end point

Secondary: On demand/rescue Therapies Post-Baseline

End point title	On demand/rescue Therapies Post-Baseline

End point description:

On Demand and/or rescue therapies were reported in the booklets by the patients.

End point type	Secondary

End point timeframe:

Between the first day after last treatment administration and 28 days after last treatment administration (study end).

End point values	EMONO - mFAS	Placebo - mFAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	103	118		
Units: subject				
At least 1 on demand/rescue therapy	57	72		
At least 1 on demand/rescue therapy (only opioids)	24	34		

Statistical analyses

No statistical analyses for this end point

Post-hoc: Total number of adverse events by timing of occurrence

End point title	Total number of adverse events by timing of occurrence

End point description:

Treatment Emergent Adverse Events (TEAEs) were categorised according to their timing of occurrence:
*Category 1: TEAEs started and ended on or before Study Day 3
*Category 2: TEAEs started or ended after Study Day 3
In case of multiple occurrences of a same preferred term for a same patient, one in category 1 (TEAEs started and ended on or before Study Day 3) and one in category 2 (TEAEs started or ended after Study Day 3), the TEAE was counted in category 2.
If study day of start of adverse event was between Day 1 and Day 3 and study day of end of adverse event was missing or if study day of start of adverse event was missing then the TEAE was classified as category 2.

End point type	Post-hoc

End point timeframe:

Between the start of first study treatment administration and study end.

End point values	EMONO	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	120		
Units: adverse event				
Treatment-emergent adverse events (TEAE)	984	414		
TEAEs started and ended on or before Study Day 3	812	318		
TEAEs started or ended after Study Day 3	172	96		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events observed from the start of study treatment until end of follow-up.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups	
Reporting group title	EMONO
Reporting group description:	
Subjects randomised in Emono arm.	
Reporting group title	Placebo
Reporting group description:	
Subjects randomised in Placebo arm.	

Serious adverse events	EMONO	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 120 (1.67%)	0 / 120 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Loss of consciousness			
subjects affected / exposed	2 / 120 (1.67%)	0 / 120 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	EMONO	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	120 / 120 (100.00%)	104 / 120 (86.67%)	
Nervous system disorders			
Somnolence			
subjects affected / exposed	99 / 120 (82.50%)	68 / 120 (56.67%)	
occurrences (all)	230	131	
Paraesthesia			

subjects affected / exposed	68 / 120 (56.67%)	28 / 120 (23.33%)	
occurrences (all)	158	40	
Depressed level of consciousness			
subjects affected / exposed	70 / 120 (58.33%)	21 / 120 (17.50%)	
occurrences (all)	144	35	
Dizziness			
subjects affected / exposed	68 / 120 (56.67%)	22 / 120 (18.33%)	
occurrences (all)	169	37	
Sensory disturbance			
subjects affected / exposed	59 / 120 (49.17%)	8 / 120 (6.67%)	
occurrences (all)	130	13	
Headache			
subjects affected / exposed	35 / 120 (29.17%)	25 / 120 (20.83%)	
occurrences (all)	61	34	
Sedation			
subjects affected / exposed	48 / 120 (40.00%)	8 / 120 (6.67%)	
occurrences (all)	90	12	
Amnesia			
subjects affected / exposed	21 / 120 (17.50%)	0 / 120 (0.00%)	
occurrences (all)	37	0	
General disorders and administration site conditions			
Feeling drunk			
subjects affected / exposed	46 / 120 (38.33%)	3 / 120 (2.50%)	
occurrences (all)	100	3	
Fatigue			
subjects affected / exposed	14 / 120 (11.67%)	17 / 120 (14.17%)	
occurrences (all)	17	18	
Asthenia			
subjects affected / exposed	7 / 120 (5.83%)	9 / 120 (7.50%)	
occurrences (all)	7	9	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	6 / 120 (5.00%)	1 / 120 (0.83%)	
occurrences (all)	8	1	
Gastrointestinal disorders			

Nausea			
subjects affected / exposed	37 / 120 (30.83%)	17 / 120 (14.17%)	
occurrences (all)	53	19	
Diarrhoea			
subjects affected / exposed	9 / 120 (7.50%)	0 / 120 (0.00%)	
occurrences (all)	11	0	
Vomiting			
subjects affected / exposed	7 / 120 (5.83%)	0 / 120 (0.00%)	
occurrences (all)	8	0	
Dry mouth			
subjects affected / exposed	6 / 120 (5.00%)	0 / 120 (0.00%)	
occurrences (all)	9	0	
Psychiatric disorders			
Euphoric mood			
subjects affected / exposed	98 / 120 (81.67%)	64 / 120 (53.33%)	
occurrences (all)	274	145	
Anxiety			
subjects affected / exposed	62 / 120 (51.67%)	34 / 120 (28.33%)	
occurrences (all)	151	61	
Confusional state			
subjects affected / exposed	36 / 120 (30.00%)	3 / 120 (2.50%)	
occurrences (all)	65	3	
Agitation			
subjects affected / exposed	21 / 120 (17.50%)	7 / 120 (5.83%)	
occurrences (all)	38	7	
Affect lability			
subjects affected / exposed	21 / 120 (17.50%)	3 / 120 (2.50%)	
occurrences (all)	29	3	
Hallucination			
subjects affected / exposed	16 / 120 (13.33%)	1 / 120 (0.83%)	
occurrences (all)	19	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 May 2017	- Authorisation of visit dates flexibility without impacting the dates of filling of the questionnaires in patient booklets, - Possibility to perform follow-up visits V5 and V6 by phone, - Addition of one non selection criterion and modification of three other non selection criteria, - Clarification about the inclusion criterion and one of the secondary objectives, - Addition of three secondary analysis criteria.
13 June 2018	- Integration of new safety data further to the update of the KALINOX TM SmPC, - Prolongation of study recruitment period to September 2018 for LPI and November 2018 for LPLV.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported