Clinical trial results:
A randomised, double-blind, placebo-controlled study to evaluate the efficacy of two different dose levels of orvepitant (10 and 30 mg) compared with placebo on EGFRi-induced intense pruritus in oncology subjects
(The “RELIEVE 1” Study)

Summary

EudraCT number	2013-002763-25
Trial protocol	IT GB
Global end of trial date	10 July 2015

Results information

Result version number	v1 (current)
This version publication date	16 July 2016
First version publication date	16 July 2016

Trial information

Trial identification

Sponsor protocol code	NT2013/Orv/Prot001

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	NeRRe Therapeutics Ltd
Sponsor organisation address	SBC, Incubator Building, Gunnels Wood Rd, Stevenage, United Kingdom, SG1 2FX
Public contact	Elizabeth Ballantyne, NeRRe Therapeutics Ltd, +44 07826 846960, Elizabeth.Ballantyne@nerretherapeutics.com
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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	29 January 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 July 2015
Global end of trial reached?	Yes
Global end of trial date	10 July 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of orvepitant (10 and 30 mg given once daily [od], orally for 4 weeks) compared with placebo in reducing the intensity of Epidermal Growth Factor Receptor Inhibitors (EGFRi)-induced intense pruritus.

Protection of trial subjects:

The study was conducted in accordance with all applicable regulatory requirements including the 'International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use' (ICH) guidelines on GCP, all applicable subject privacy requirements, and, the guiding principles of the Declaration of Helsinki and all applicable amendments laid down by the world assemblies. This included, but was not limited to, the following:
- IRB/IEC review and favourable opinion/approval to conduct the study and of any subsequent relevant amended documents
- Written informed consent (and any amendments) to be obtained from each subject before participation in the study
- Investigator reporting requirements (e.g. reporting of AEs/SAEs to IRB/IEC).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 November 2013
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	United Kingdom: 4
Country: Number of subjects enrolled	Italy: 40
Worldwide total number of subjects	44
EEA total number of subjects	44

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	32
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Adult patients experiencing intense pruritus symptoms following treatment with any EGFRi medicines for malignant solid tumours. Patients were not to have received treatment for any other type of pruritus within the previous 3 months.

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

Blinding implementation details:

This was a double-blind study in which orvepitant 30 mg, orvepitant 10 mg and matching placebo were identical in appearance and presented as white round tablets.
The randomization number for each patient was provided at the Baseline visit via randomization by connection to the Interactive Response Technology (IRT).
The randomization schedule was not to be broken until the study has completed and all data queries were resolved.

Arms

Are arms mutually exclusive?	Yes
Arm title	Orvepitant 10 mg Tablet

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Orvepitant 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

10 mg orvepitant tablets administered once daily for 4 weeks.

Arm title	Orvepitant 30 mg Tablet

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Orvepitant 30 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Orvepitant 30 mg Tablets once daily for 4 weeks.

Arm title	Placebo

Arm description: -

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Once daily for 4 weeks.

Number of subjects in period 1	Orvepitant 10 mg Tablet	Orvepitant 30 mg Tablet	Placebo
Started	14	16	14
Completed	11	12	12
Not completed	3	4	2
Consent withdrawn by subject	1	1	-
Adverse event, non-fatal	1	1	-
EGFRi dose reduction / delay	1	-	1
Disease Progression	-	1	1
Protocol deviation	-	1	-

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	44	44	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	12	12	
From 65-84 years	32	32	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	18	18	
Male	26	26	
Race Units: Subjects			
Caucasian	44	44	

End points

End points reporting groups	
Reporting group title	Orvepitant 10 mg Tablet
Reporting group description: -	
Reporting group title	Orvepitant 30 mg Tablet
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: Change in Pruritus Intensity from Baseline to Week 4	
End point title	Change in Pruritus Intensity from Baseline to Week 4
End point description: Change in pruritus intensity assessed by patient-recorded numerical rating score.	
End point type	Primary
End point timeframe: Change from Baseline to Week 4.	

End point values	Orvepitant 10 mg Tablet	Orvepitant 30 mg Tablet	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	13	14	
Units: N/a				
arithmetic mean (standard deviation)	-3.04 (± 3.062)	-2.78 (± 2.644)	-3.21 (± 1.768)	

Statistical analyses

Statistical analysis title	Orvepitant 30 mg v Placebo
Comparison groups	Orvepitant 30 mg Tablet v Placebo
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.12
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.35
upper limit	2.95

Statistical analysis title	Orvepitant 10 mg v Placebo
Comparison groups	Orvepitant 10 mg Tablet v Placebo
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.194
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.62
upper limit	2.96

Adverse events

Adverse events information	
Timeframe for reporting adverse events: AEs were collected from the moment the ICF was signed until the Follow-up visit.	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0
Reporting groups	
Reporting group title	Orvepitant 10 mg Tablet
Reporting group description: -	
Reporting group title	Orvepitant 30 mg Tablet
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Orvepitant 10 mg Tablet	Orvepitant 30 mg Tablet	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 14 (0.00%)	0 / 16 (0.00%)	0 / 14 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Frequency threshold for reporting non-serious adverse events: 0.05 %

Non-serious adverse events	Orvepitant 10 mg Tablet	Orvepitant 30 mg Tablet	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 14 (92.86%)	11 / 16 (68.75%)	10 / 14 (71.43%)
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 14 (14.29%)	3 / 16 (18.75%)	3 / 14 (21.43%)
occurrences (all)	2	5	3
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 14 (7.14%)	2 / 16 (12.50%)	0 / 14 (0.00%)
occurrences (all)	1	3	0
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	0 / 14 (0.00%)	1 / 16 (6.25%)	3 / 14 (21.43%)
occurrences (all)	0	1	3
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 14 (7.14%)	1 / 16 (6.25%)	1 / 14 (7.14%)
occurrences (all)	1	1	1
Skin and subcutaneous tissue disorders			
Skin toxicity			
subjects affected / exposed	3 / 14 (21.43%)	2 / 16 (12.50%)	2 / 14 (14.29%)
occurrences (all)	4	3	5
Rash			
subjects affected / exposed	3 / 14 (21.43%)	0 / 16 (0.00%)	0 / 14 (0.00%)
occurrences (all)	3	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 April 2014	Protocol Amendment Number 01 (Protocol Version 2.0, dated 29 April 2014): This protocol amendment included the following: - Inclusion Criteria modified to allow patients with a moderate level of EGFRi-induced pruritus to be recruited as reflected by a reduction of the Numerical Rating Scale (NRS) score at entry from ≥ 7 to ≥ 5. - Removal of measurement of Substance P as an Exploratory Biomarker. - Afatinib (Giotrif®) added to the list of approved EGFRi monotherapies in the Inclusion Criteria. - Minor updates made to reflect changes in the Medical Monitor and Sponsor Contact Information personnel. - Addition of details about the Data Safety Monitoring Board (DSMB).
12 August 2014	Protocol Amendment Number 02 (Protocol Version 2.1, dated 12 August 2014): This was a UK specific amendment to address the medical points raised in a 'nonacceptance' letter from the MHRA. Specifically, these were to: - Add further detail regarding actions to be taken for unblinding in the event of a medical emergency. - Provide cautionary information relating to a potential cytochrome P450 3A4 drug-drug interaction (DDI) risk with orvepitant when co-administered with drugs with a narrow therapeutic window primarily metabolised by the same route.
24 February 2015	Protocol Amendment Number 03 (Protocol Version 3.0 dated 24 February 2015): This amendment included: - Removal of 10 mg dose arm - Reduction of number of patients from a total of 30 patients randomised to each of 3 arms, to 20 patients randomised to each of 2 arms arm (to give a total of 17 patients completing dosing and critical assessments in each arm). This was based on a reduction in the power of the study to 80% from 90% consistent with that needed for an investigational medicine study at the Phase II stage of development. - Option added for patients to use a Paper Diary for their patient-reported NRS scores, instead of the NRS-IVRS. - Insomnia medication removed from list of prohibited medications. - Double-barrier method removed from the list of acceptable contraceptive methods as this is not recognised as a highly effective birth control method. - The allowable window for the Week 1 (Visit 3) visit was extended by 1 day. - Chief Medical Officer (CMO) – Dr Ajay Duggal added as signatory to the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported