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The neurokinin-1 antagonist orvepitant for EGFRI-induced pruritus in cancer patients: a randomised, placebo-controlled, phase II trial

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TITLE: The neurokinin-1 antagonist orvepitant for EGFRI-induced pruritus in cancer patients: a randomised, placebo-controlled, phase II trial

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ABSTRACT

Objective To evaluate the efficacy of orvepitant (10 or 30 mg given once daily, orally for 4 weeks), a neurokinin-1 antagonist, compared with placebo in reducing the intensity of epidermal growth factor receptor inhibitor (EGFRI)-induced intense pruritus

Design Randomised, double-blind, placebo-controlled clinical trial

Setting 15 hospitals in Italy and 5 hospitals in the United Kingdom

Participants 44 patients aged ≥18 years receiving an EGFRI for a histologically confirmed malignant solid tumour and experiencing moderate or intense pruritus after EGFRI treatment

Intervention 30 mg or 10 mg orvepitant or placebo tablets once daily for 4 weeks (randomised 1:1:1)

Primary and secondary outcome measures Numerical rating scale (NRS) from 0 (no itch) to 10 (worst itch imaginable) daily between Baseline and Week 8; NRS, verbal rating scale, Skindex-16, and Leeds Sleep Evaluation Questionnaire at each study visit (Baseline, Week 1, Week 4, Week 8); assessment and grading of EGFRI-induced rash at Baseline, Week 4, Week 8

Results Mean NRS change from Baseline to Week 4 was -2.78 (SD: 2.64) points in the 30 mg group, -3.04 (SD: 3.06) points in the 10 mg group, and -3.21 (SD: 1.77) points in the placebo group; the difference between orvepitant and placebo was not statistically significant. The trial was terminated early because of recruitment challenges; only 44 of the planned 90 patients were randomised. All patients were analysed for efficacy and safety. No safety signal was detected. Adverse events related to orvepitant (asthenia, dizziness, dry mouth, hyperhidrosis) were all of mild or moderate severity.

Conclusions Orvepitant was safe and well tolerated. No difference in NRS score between the orvepitant and placebo groups was observed at Week 4. Other than a true lack of efficacy, potential explanations for this finding include early termination, placebo effect, or natural progression of the condition.

Trial registration number EudraCT 2013-002763-25

KEY WORDS: pruritus, EGFR inhibitor, neurokinin-1 antagonist, orvepitant

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The RELIEVE 1 study was the first randomised, double-blind, placebo-controlled study of a neurokinin-1 antagonist for EGFRI-induced pruritus.
- The RELIEVE 1 study provided insights into the course and itch characteristics of EGFRI-induced pruritus.
- The critically ill patients treated in this study may have had particularly high expectations for a benefit from the treatment, which may have contributed to response in both placebo and active groups.
- The enrolment target was not reached because of recruitment problems in the critically ill target population.

INTRODUCTION

While targeted biological therapies have increased patient survival for several tumour types, they have been associated with a variety of adverse events (AEs), particularly dermatological AEs including pruritus. In a 2013 systematic review and meta-analysis of pruritus with targeted cancer therapies, the incidences of all-grade and high-grade pruritus were 17.4% and 1.4%, respectively, and the relative risk of all-grade pruritus was 2.90.[1] A 2015 systematic review and meta-analysis reported that panitumumab and gefitinib showed the highest incidences of all-grade pruritus (56.8% and 49.4%, respectively) and sunitinib and erlotinib the lowest (5.8% and 3.6%, respectively). The relative risk of development for all-grade pruritus in this study was 2.2 and for high-grade pruritus 2.6. Anti-epidermal growth factor receptor inhibitor (EGFRI) monoclonal antibodies (mAbs) had the highest relative risk of all-grade pruritus of 2.84 compared to EGFR/HER2 tyrosine kinase inhibitors and 1.24 compared to immunotherapy.[2] Both reports emphasise the importance of pruritus management in cancer patients and advise patient education and counselling, frequent clinical monitoring, and timely treatment to prevent more significant outcomes such as excoriations or infections and to optimise targeted therapy dosing.

EGFRIs have specifically been associated with a number of dermatological AEs (including acneiform rash, hair changes. mucositis, xerosis/fissures, and paronychia as well as pruritus) that can require dose modification or treatment interruptions and thus interfere with these potentially life-prolonging therapies.[3-7] Rash, xerosis, and pruritus have the greatest impact on patient quality of life.[7-9] Pruritus incidence reported in clinical trials of anti-EGFR mAbs and small-molecule EGFRIs varies from 10% to 16% for cetuximab, 57% to 69% for panitumumab, 9% to 13% for erlotinib, 8% to 9% for gefitinib, 28% to 45% for lapatinib, and 14% for osimertinib.[10-11] EGFRI-induced pruritus may be underreported or incompletely reported in clinical studies.[12] In a survey of 379 cancer survivors (112 on targeted therapies), 36% experienced pruritus during treatment, and of the 122 patients whose quality of life was diminished by a treatment side effect, 44% attributed this effect to pruritus.[13] Lacouture et al. reported that pruritus occurs in approximately half of all patients treated with EGFRIs.[6] Finally, in a review of interviews conducted with 100 patients taking mainly EGFR mAbs, 72% of patients reported experiencing pruritus.[14]

Neurokinin-1 (NK1) receptor antagonists are a promising therapy for acute and chronic EGFRI-induced pruritus.[15] Gerber et al. reported that mast cells significantly accumulate in the lesional skin of patients treated with EGFRIs and suggested that the antipruritic activity of the NK1 receptor antagonist aprepitant is achieved by blocking the activation of mast-cell NK1 receptors by its cognate ligand substance P, thereby preventing the release of mast cell histamine and other proinflammatory/pruritogenic mediators.[16-18] Aprepitant (Emend®) is the first commercially available drug of a new class of NK1 receptor antagonists for the prevention of chemotherapy-induced and postoperative nausea and vomiting. It has been evaluated in numerous open-label clinical studies of patients suffering from treatment-refractory pruritus, including a large number of patients suffering with acute EGFRI-induced pruritus.[19-33] Aprepitant is a rapid and highly effective antipruritic medication that significantly improves patients' quality of life. The 2015 systematic review and meta-analysis advocated the testing of aprepitant and other emerging NK1 receptor antagonists in patients receiving agents with a high risk of pruritus.[2] Orvepitant, a potent and selective NK1 antagonist that blocks substance P activity, has a similar mechanism of action to aprepitant and thus may be expected to achieve similar antipruritic efficacy in patients suffering from intense itch. The RELIEVE 1 study was the first randomised, double-blind, placebo-controlled study of an NK1 antagonist for EGFRI-induced pruritus.

METHODS

Study design and enrolment

The primary objective of this Phase 2, multicentre, randomised, double-blind, placebo-controlled clinical trial was to evaluate the efficacy of orvepitant compared with placebo in reducing the intensity of intense EGFRI-induced

pruritus. Pruritus intensity was measured primarily by change from Baseline in patient-recorded numerical rating scale (NRS) score ranging from 0 (no itch) to 10 (worst itch imaginable) points. On the basis of an assumed between-patient standard deviation (SD) of 2 points,[10] 23 patients per treatment arm were required to provide 80% power for a 2-sided 5% significance level hypothesis test to achieve a significant result when the true difference is at least 2 points. It was thus planned to enrol 30 patients per arm (90 total). After 20 months of recruitment, this target was far from being reached, and a blinded analysis of data variance indicated that it was highly unlikely that a statistically robust assessment of benefit could be made even if enrolment were completed. The sponsor decided to terminate enrolment. However, the study data for all enrolled patients were analysed.

Patients and treatments

Patients were enrolled at 15 hospitals in Italy and 5 hospitals in the United Kingdom between 13 November 2013 and 11 May 2015. Key eligibility criteria were age 18 years and older, monotherapy with an EGFRI (including cetuximab, panitumumab, erlotinib, gefitinib, lapatinib, and afatinib) for a histologically confirmed malignant solid tumour, moderate or intense pruritus after treatment with the EGFRI (defined as the mean of between 2 and 7 daily patient-reported average pruritus intensity NRS scores initially ≥7 and subsequently changed in April 2014 to ≥5 to improve study recruitment), pruritus treatment within the previous 3 months, and no use of aprepitant or fosaprepitant in the previous 4 weeks. The investigators randomised eligible patients according to a central randomisation code generated by the sponsor using an interactive voice response system (IVRS). The patients were assigned in a 1:1:1 ratio to receive 30 mg orvepitant, 10 mg orvepitant, or placebo tablets once daily (in the evening before bedtime) for 4 weeks. Randomisation was stratified by investigational site; block size was 6. Placebo tablets were identical in appearance to orvepitant tablets.

Assessments

Patients were followed-up for 4 weeks after treatment was completed or discontinued. Patients reported their NRS score daily using an IVRS between Baseline and Week 8, and at each study visit (Baseline, Week 1, Week 4, Week 8) they completed a study visit NRS and a verbal rating scale (VRS) (validated instruments for the measurement of pruritus intensity),[34] the Skindex-16 (an instrument to measure the effects of skin disease on health-related quality of life),[35] and the Leeds Sleep Evaluation Questionnaire (LSEQ; a 10-item instrument to assess changes in sleep quality over the course of an intervention). EGFRI-induced rash was assessed and graded at Baseline, Week 4, and Week 8. Safety was assessed by physical examination (including Eastern Cooperative Oncology Group [ECOG] status) and 12-lead electrocardiogram (ECG) at Baseline and Week 8, vital signs and laboratory tests (haematology, serum biochemistry, urinalysis) at each visit, and recording of AEs throughout the study. AEs were graded and categorised according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE). Use of concomitant medications, including EGFRIs and any rescue medication, was recorded throughout the study.

Endpoints

The primary endpoint was change from Baseline in mean patient-recorded NRS score (over the last 3 recordings) at Week 4. Secondary endpoints were also evaluated: change from Baseline in mean patient-recorded NRS score (last 3 recordings) at Weeks 1, 4, 8; change from Baseline in mean patient-recorded NRS score (all week) at Weeks 1, 4, 8; change from Baseline in clinic visit NRS score at Weeks 1, 4, 8; change from Week 4 in patient-recorded NRS score at Weeks 5, 6, 7, 8; change from Baseline in clinic visit VRS score at Weeks 1, 4, 8; change from Week 4 in clinic visit VRS score at Week 8; change from Baseline in pruritus intensity (from patient-recorded NRS) at Days 2, 3, 4, 5, 6, 7, 8; change from Baseline in Skindex-16 at Weeks, 1, 4, 8; change from Baseline in LSEQ at Weeks, 1, 4, 8; rescue medication use; EGFRI dose reduction; and study withdrawal because of intense uncontrolled pruritus.

Statistical analysis

Efficacy endpoints were analysed in the intention-to-treat (ITT) population of all randomised patients who had received at least the first dose of study medication and had at least 1 post-treatment efficacy assessment. The primary endpoint was analysed by mixed-model repeated measures analysis with the primary inference being the change from Baseline in patient-reported NRS-scores averaged across the last 3 values of the fourth week of dosing fitted as the response variable in the mixed model. Point estimates and corresponding 95% confidence intervals were constructed for the difference between each dose of orvepitant and placebo for each week. Safety was analysed in the safety population of all patients who received a dose of study medication using descriptive statistics.

Patient and Public Involvement

Patients and public were not involved in the design, conduct and reporting of this clinical research.

RESULTS

Patients

A total of 44 patients were randomised and treated: 16 to orvepitant 30 mg, 14 to orvepitant 10 mg, and 14 to placebo. Nine patients discontinued the study (Figure 1). All patients were Caucasian, and 26 (59%) were male and 18 (41%) female. Median age was 68 years (range: 35 to 83 years), and 32 (73%) patients were aged 65 or older. Mean baseline NRS ranged from 5.88 (SD: 0.93) in the placebo group to 6.68 (SD: 1.28) in the 30 mg orvepitant group. At Baseline, most patients had moderate to severe pruritus, and the most common locations were the head (26 [59%] patients) and the trunk (11 [25%]). Baseline assessments of acneiform rash and maculopapular rash showed a similar pattern (Table 1).

Table 1. Demographic and baseline characteristics

Characteristic	Orvepitant 30 mg *N* = 16	Orvepitant 10 mg *N* = 14	Placebo *N* = 14	Total *N* = 44
Age (years), median (range)	69.0 (43, 83)	73.5 (49, 81)	67.0 (35, 76)	68.0 (35, 83)
Age groups, n (%)				
< 65 years	4 (25.0)	4 (28.6)	4 (28.6)	12 (27.3)
≥ 65 years	12 (75.0)	10 (71.4)	10 (71.4)	32 (72.7)
Gender, n (%)				
Female	5 (31.3)	5 (35.7)	8 (57.1)	18 (40.9)
Male	11 (68.8)	9 (64.3)	6 (42.9)	26 (59.1)
Race, n (%)				
Caucasian	16 (100.0)	14 (100.0)	14 (100.0)	44 (100.0)
Time since cancer diagnosis (months), median (range)	17.5 (1, 131)	29.7 (12, 129)	20.8 (5, 60)	23.0 (1, 131)
Patient-reported NRS				
Mean (SD)	6.68 (1.278)	6.95 (1.4.13)	5.88 (0.930)	NC
Median (range)	6.86 (4.8, 9.3)	7.00 (5.0, 10.0)	5.57 (5.0, 7.4)	NC
PRURITUS				
CTCAE grade, n (%)				

Grade 1	2 (12.5)	0	0	2 (4.5)
Grade 2	8 (50.0)	9 (64.3)	11 (78.6)	28 (63.6)
Grade 3	5 (31.3)	5 (35.7)	3 (21.4)	13 (29.5)
Unknown	1 (6.3)	0	0	1 (2.3)
Location, n (%)				
Head	8 (50.0)	6 (42.9)	12 (85.7)	26 (59.1)
Trunk	7 (43.8)	3 (21.4)	1 (7.1)	11 (25.0)
Arms	0	3 (21.4)	0	3 (6.8)
Legs	0	2 (14.3)	1 (7.1)	3 (6.8)
Unknown	1 (6.3)	0	0	1 (2.3)
ACNEIFORM RASH				
CTCAE grade, n (%)				
Grade 1	2 (12.5)	3 (21.4)	2 (14.3)	7 (15.9)
Grade 2	7 (43.8)	7 (50.0)	10 (71.4)	24 (54.5)
Grade 3	6 (37.5)	3 (21.4)	1 (7.1)	10 (22.7)
Unknown	1 (6.3)	1 (7.1)	1 (7.1)	3 (6.8)
Location, n (%)				
Head	7 (43.8)	5 (35.7)	11 (78.6)	23 (52.3)
Trunk	7 (43.8)	5 (35.7)	0	12 (27.3)
Arms	1 (6.3)	3 (21.4)	1 (7.1)	5 (11.4)
Legs	0	0	1 (7.1)	1 (2.3)
Unknown	1 (6.3)	1 (7.1)	1 (7.1)	3 (6.8)
MACULOPAPULAR RASH				
CTCAE grade, n (%)				
Grade 1	3 (18.8)	5 (35.7)	5 (35.7)	13 (29.5)
Grade 2	8 (50.0)	5 (35.7)	8 (57.1)	21 (47.7)
Grade 3	4 (25.0)	3 (21.4)	0	7 (15.9)
Unknown	1 (6.3)	1 (7.1)	1 (7.1)	3 (6.8)
Location, n (%)				
Head	7 (43.8)	5 (35.7)	12 (85.7)	24 (54.5)
Trunk	7 (43.8)	4 (28.6)	0	11 (25.0)
Arms	1 (6.3)	4 (28.6)	0	5 (11.4)
Legs	0	0	1 (7.1)	1 (2.3)
Unknown	1 (6.3)	1 (7.1)	1 (7.1)	3 (6.8)

CTCAE = Common Terminology Criteria for Adverse Events; NC = not calculated; NRS = numerical rating scale; SD = standard deviation.

The median dose number was 28 (range: 1 to 35) in the 30 mg group, 28 (range: 1 to 35) in the 10 mg group, and 29 (range: 28 to 39) in the placebo group. Five (11%) patients (all in the orvepitant groups) took the study drug for 1 week or less; 18 (41%) patients took the study drug (orvepitant or placebo) for 1 to 4 weeks, and 21 (48%) took the study drug for >4 weeks (maximum: 39 days).

All 44 patients were included in the ITT and safety populations and analysed according to the randomised treatment.

Efficacy

Patient compliance with daily reporting of NRS score was high; mean compliance rate was 92%, and median compliance rate was 100%. At Week 4, 38 subjects remained in the study. NRS score decreased from Baseline to Week 4 in all 3 groups (Table 2).

Table 2. Change from baseline in patient-reported numerical reporting scale scores at Week 4

Statistic	Orvepitant 30 mg *N* = 16	Orvepitant 10 mg *N* = 14	Placebo *N* = 14
n	**13**	**11**	**14**
Mean (SD)	-2.78 (2.644)	-3.04 (3.062)	-3.21 (1.768)
Median	-2.75	-2.00	-2.50
Minimum, maximum	-6.3, 3.0	-8.3, 1.1	-6.3, 0.0
LSMEANS estimate (95% CI)	-2.40 (-3.54, -1.27)	-2.53 (-3.80, -1.27)	-3.70 (-4.88, -2.52)
LSMEANS standard error (95% CI)	0.560	0.623	0.577
Orvepitant vs placebo difference (95% CI)	1.30 (-0.35, 2.95)	1.17 (-0.62, 2.96)	
P value	0.120	0.194	
CI = confidence interval; LSMEANS = least-squares means; SD = standard deviation.			

The difference between orvepitant and placebo was not statistically significant (30 mg group: $P = 0.12$, 10 mg group: $P = 0.19$). Secondary NRS and VRS endpoints reflected the results for the primary endpoint (Supplemental Table 1). Change from Baseline in Skindex-16 and LSEQ score showed no difference between the treatment groups at any time point. Seven (15.9%) patients (3 in the orvepitant 30 mg group and 2 each in the orvepitant 10 mg and placebo groups) used rescue medications during the study.

Safety

No safety signal was detected. A total of 34 (77%) patients experienced a treatment-emergent AE, but no unexpected AEs were noted. The only AEs that occurred in >5% of patients were asthenia (8 [18%] patients), skin toxicity (7 [16%] patients; term reported by the investigators was skin toxicity, which for EGFRIs commonly includes reactions such as skin rash, skin dryness [xerosis], pruritus, paronychia, hair abnormality, mucositis, and increased, growth of the eyelashes or facial hair[36]), diarrhoea (4 [9%] patients), cough (3 [7%] patients), rash (3 [7%] patients; terms as reported by the investigators included worsening of rash; hands, ankle and face rash; and rash cutaneous), and anaemia (3 [7%] patients). Other than anaemia and rash, which occurred only in patients who received orvepitant, these more common AEs occurred in similar rates in the active and placebo groups. There was no apparent relationship between incidence or severity of AEs and orvepitant dose. No serious AEs were reported. Only 4 mild and moderate AEs were considered related to orvepitant (Table 3).

Table 3. Drug-related adverse events

	Orvepitant 30 mg *N* = 16 n (%)	Orvepitant 10 mg *N* = 14 n (%)	Placebo *N* = 14 n (%)
Any drug-related AE	3 (18.8)	1 (7.1)	0
Mild AEs			
Asthenia	1 (6.3)	0	0

Dizziness	0	1 (7.1)	0
Dry mouth	1 (6.3)	0	0
Moderate AEs			
Hyperhidrosis	1 (6.3)	0	0

No clinically significant changes in laboratory results, vital signs, physical examination findings, ECOG status, or ECG parameters were related to orvepitant.

DISCUSSION

Orvepitant appeared safe and well tolerated in this study, and the safety profile exhibited allows further investigation of orvepitant in this or other indications.

The efficacy results in this randomized, double-blind, placebo-controlled study were inconclusive. No difference between the active groups and the placebo group was observed. It is important to consider the potential causes for this lack of difference to inform further research in this indication. Other than a true lack of efficacy, this finding may have resulted from the premature termination of the study and the consequent substantially reduced sample size. Another potential explanation is a placebo effect. A placebo effect is often seen with subjective endpoints such as pruritus intensity, and a recent meta-analysis of clinical trials showed that placebo has a substantial effect in in patients suffering from chronic itch.[37] Placebo effects in clinical trials result from the expectation by patients and their physicians of the potential benefit of the investigational drug. In this study, critically ill patients were receiving a modern antineoplastic therapy. It might be true that these patients have a particularly high expectation of the benefit of their EGFRI therapy in general and of orvepitant's ability to reduce pruritus and thereby enable prolongation of their EGFRI therapy. Thus, it might be very difficult to study a treatment for an expectation-driven symptom in this patient population. The improvement seen in the 2 orvepitant groups and the placebo group may have also been the result of the natural course of this acute pruritus condition, which is not well defined at this time.

Nevertheless, NK1 antagonists still hold potential for treatment of skin toxicities experienced by cancer patients treated with EGFRIs or other targeted therapies. In a randomised, placebo-controlled clinical trial of serlopitant in patients with prurigo nodularis, serlopitant reduced itch as reported on a visual analogue scale after 4 and 8 weeks of treatment and was superior to placebo in multiple secondary pruritus endpoints.[38] Further randomised, placebo-controlled trials of NK1 antagonists are needed to evaluate findings in observational studies, but the experience of this trial, recruitment difficulty and improvement in patients' pruritus regardless of treatment assignment, shows that further research in this indication will prove challenging. Recruitment for this study was stopped after 20 months when only 44 of the planned 90 subjects had been enrolled. Despite evidence in the literature of a high prevalence of EGFRI-induced pruritus,[1-14,39] we experienced substantial difficulty identifying patients with severe enough pruritus (i.e., NRS score ≥ 5) to enable detection of post-treatment change. Study enrolment may have been limited by the fact that all investigators were oncologists, who are faced with multiple AEs in patients receiving EGFRIs (e.g., diarrhea, rash, asthenia, nausea and vomiting, conjunctivitis, mucositis) that may have taken precedence over pruritus, a purely subjective symptom that is not widely reported in the oncology community.[12] Future studies will require a more complete understanding of the epidemiology and course of target cancer therapy-induced pruritus, a sufficient and appropriate patient population to achieve statistical power, and a design that minimises or quantifies a potential placebo effect.

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Contributors Study concept and design: BV, MT, PH, ML, ER, GT, AW, SS; data acquisition: BV, PG; quality control of data and algorithms: PH, DJ; data analysis and interpretation: BV, MT, AD, SS; statistical analysis: DJ; manuscript preparation: MT; manuscript editing: BV, SS. All authors read, edited, and approved the final manuscript.

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Competing interests MT is a current employee and ER is a past employee of NeRRe Therapeutics Ltd. BV and PG received payment from NeRRe as investigators in this study. AD received payment from NeRRe for service as the Chief Medical Officer for this study. DJ is an employee of Cromsource, which received payment from NeRRe for statistical analysis of this study. PH has received payment from NeRRe as a consultant. ML reports receiving personal fees from Legacy Healthcare Services, AdgeroBio Pharmaceuticals, Amryt Pharma, Celldex Therapeutics, Debiopharm, Galderma Research and Development, Johnson & Johnson, Novocure, Lindi Skin, Merck Sharp and Dohme Corporation, Helsinn Healthcare SA, Janssen Research & Development LLC , Menlo Therapeutics, Novartis Pharmaceuticals Corporation, F. Hoffmann-La Roche AG, Abbvie Inc. Boehringer Ingelheim Pharma Gmbh & Co. KG, Allergan Inc, Amgen Inc, E.R. Squibb & Sons L.L.C., EMD Serono Inc, AstraZeneca Pharmaceuticals LP, Genentech Inc, Leo Pharma Inc, Seattle Genetics, Bayer, Männer SAS, Lutris Pharma, Pierre Fabre, Paxman Cooler Ltd, Adjucare, Dignitana, Biotechspert, Teva Pharmaceuticals Mexico, Parexel, OnQuality Pharmaceuticals Ltd, Novartis, Our Brain Bank, Millenium Pharmaceuticals and research funding from Berg Health, Bristol-Myers Squibb, Lutris Pharma, Novocure, Paxman, Biotest, and Veloce BioPharma. GT reports no conflicts of interest. AW reports receiving payment from NeRRe as Chair of the Advisory Board and from Advent Life Sciences for consultancy, Canbex Therapeutics as a nonexecutive director (past position), Calcico Therapeutics as chairman (past position) and a nonexecutive director, and the Wellcome Trust as a member of grant committees. SS reports receiving payment from NeRRe as a member of the advisory board and from Almirall, Astellas Pharma, Beiersdorf, Celgene Corporation, Chugai Pharma, Creabilis, Daiichi Sankyo, Galderma, Helsinn, Kiniska Pharmaceuticals, Kneipp, Maruho Co, Merz Pharma, Novartis, Pierre Fabre Laboratories, Sienna Biopharmaceuticals, and Ziarco as a member of their advisory boards and from Menlo Therapeutics as an investigator and participation as an investigator in trials sponsored by Dermascence, Trevi Therapeutics, and Vanda Pharmaceuticals.

Patient consent All patients provided written informed consent for participation before enrolment in the trial.

Ethics approval This trial was approved by Ethics Committees for all investigational sites.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The deidentified data set for this study is available upon reasonable request from the study sponsor NeRRe Therapeutics Ltd.

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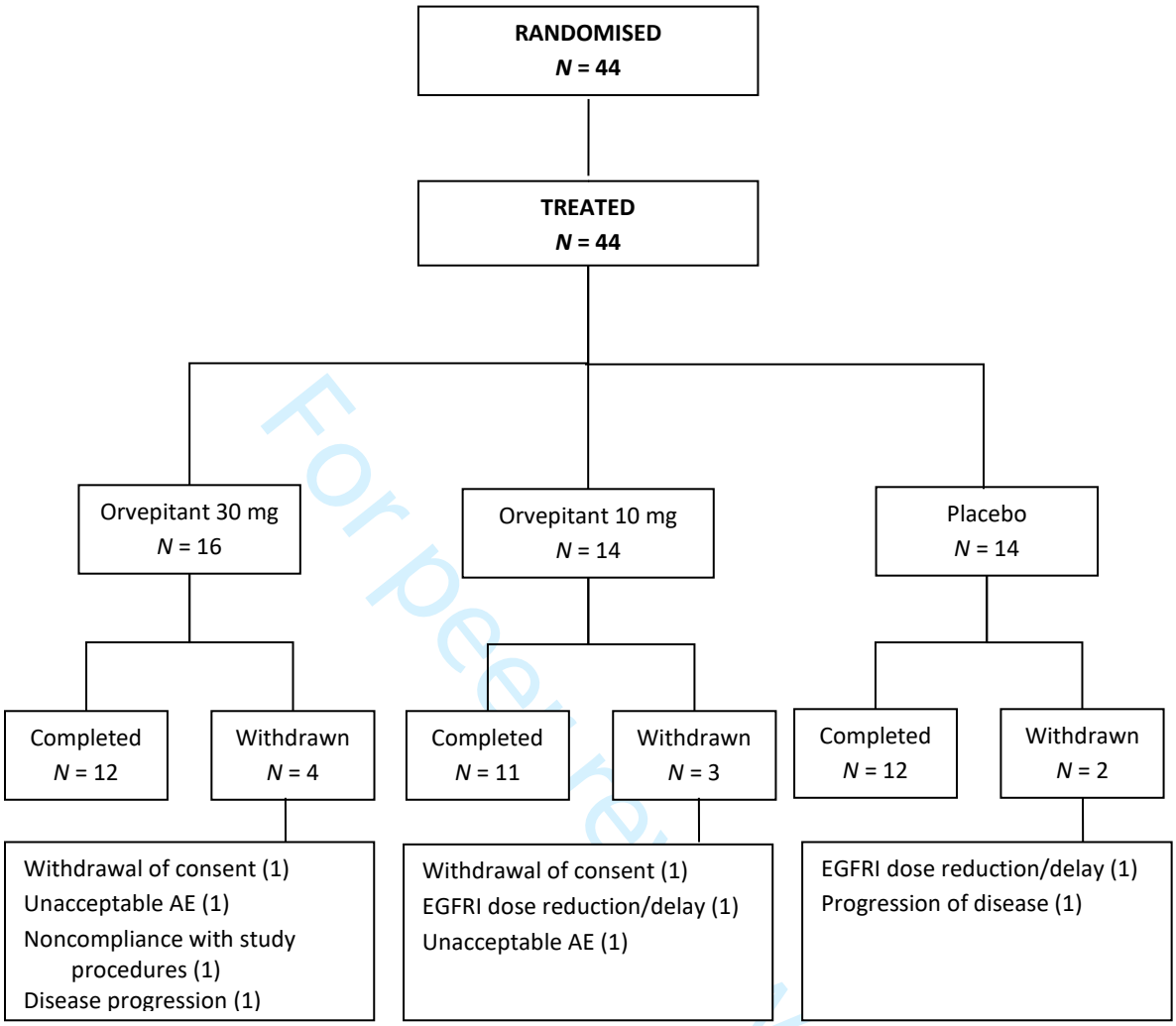

Supplemental Table 1. Summary of secondary efficacy endpoints

Statistic	Orvepitant 30 mg *N* = 16	Orvepitant 10 mg *N* = 14	Placebo *N* = 14
Change from Baseline, (n) Mean (SD)			
Mean patient-recorded NRS score (last 3 recordings) at Week 1	(16) -1.18 (1.547)	(13) -1.66 (2.477)	(14) -1.16 (1.407)
Mean patient-recorded NRS score (last 3 recordings) at Week 4	(13) -2.78 (2.644)	(11) -3.04 (3.062)	(14) -3.21 (1.768)
Mean patient-recorded NRS score (last 3 recordings) at Week 8	(11) -2.86 (2.907)	(10) -3.18 (2.676)	(12) -4.32 (2.272)
Mean patient-recorded NRS score (all week) at Week 1	(16) -0.96 (1.094)	(13) -1.34 (1.933)	(14) -0.86 (1.002)
Mean patient-recorded NRS score (all week) at Week 4	(13) -2.64 (2.613)	(11) -3.05 (2.998)	(14) -3.20 (1.961)
Mean patient-recorded NRS score (all week) at Week 8	(11) -2.65 (2.810)	(10) -3.15 (2.663)	(12) -4.29 (2.328)
Clinic visit NRS score at Week 1	(14) -1.93 (1.730)	(14) -2.21 (3.191)	(14) -3.00 (2.602)
Clinic visit NRS score at Week 4	(13) -3.38 (2.694)	(11) -4.27 (2.936)	(14) -4.14 (2.179)
Clinic visit NRS score at Week 8	(13) -3.50 (2.714)	(11) -3.91 (2.663)	(12) -3.92 (2.353)
Pruritus intensity (from patient-recorded NRS) at Day 2	(16) -0.61 (1.287)	(12) -0.84 (1.242)	(13) -0.33 (0.735)
Pruritus intensity (from patient-recorded NRS) at Day 3	(14) -0.96 (0.985)	(11) -0.86 (1.638)	(13) -0.41 (0.647)
Pruritus intensity (from patient-recorded NRS) at Day 4	(14) -0.85 (1.093)	(12) -1.04 (1.880)	(14) -0.81 (1.276)
Pruritus intensity (from patient-recorded NRS) at Day 5	(13) -1.35 (1.120)	(12) -1.29 (2.229)	(13) -1.18 (1.453)
Pruritus intensity (from patient-recorded NRS) at Day 6	(14) -1.28 (1.680)	(11) -1.31 (2.203)	(11) -1.30 (1.544)
Pruritus intensity (from patient-recorded NRS) at Day 7	(14) -1.42 (2.300)	(12) -1.87 (3.626)	(13) -1.33 (1.886)
Pruritus intensity (from patient-recorded NRS) at Day 8	(14) -1.85 (2.305)	(11) -1.83 (2.417)	(14) -1.88 (2.027)
Skindex-16 at Week 1: Symptoms	(14) -12.56 (22.253)	(13) 1.24 (25.053)	(13) -2.88 (18.502)
Skindex-16 at Week 4: Symptoms	(13) -8.29 (25.056)	(11) -9.09 (36.936)	(13) -7.69 (29.558)
Skindex-16 at Week 8: Symptoms	(12) -8.09 (23.603)	(11) -8.71 (36.190)	(12) -4.02 (33.301)
Skindex-16 at Week 1: Emotions	(14) -44.73 (16.352)	(13) -21.52 (27.804)	(13) -21.29 (18.203)
Skindex-16 at Week 4: Emotions	(13) -32.60 (24.955)	(11) -31.96 (36.342)	(13) -25.69 (26.543)
Skindex-16 at Week 8: Emotions	(12) -35.37 (30.875)	(11) -37.23 (28.133)	(12) -36.86 (26.317)
Skindex-16 at Week 1: Functioning	(14) -13.33 (16.692)	(13) -12.05 (29.078)	(13) -1.28 (13.508)
Skindex-16 at Week 4: Functioning	(13) 2.05 (26.511)	(11) -11.51 (36.066)	(13) -1.80 (20.395)
Skindex-16 at Week 8: Functioning	(12) -0.83 (28.038)	(11) -22.73 (25.638)	(12) -5.00 (16.174)

LSEQ at Week 1: Getting to sleep	(13) -12.08 (22.103)	(12) -9.82 (23.495)	(12) -6.45 (16.971)
LSEQ at Week 4: Getting to sleep	(12) -12.36 (19.608)	(9) 3.37 (23.642)	(12) -8.47 (18.190)
LSEQ at Week 8: Getting to sleep	(11) -4.57 (13.665)	(9) 2.04 (25.470)	(11) -7.06 (23.678)
LSEQ at Week 1: Quality of sleep	(13) -6.77 (26.983)	(12) -13.29 (33.394)	(12) -5.67 (15.389)
LSEQ at Week 4: Quality of sleep	(12) -6.46 (20.633)	(9) -8.61 (39.094)	(12) -9.13 (17.601)
LSEQ at Week 8: Quality of sleep	(11) -6.46 (20.633)	(9) -8.61 (39.094)	(11) -9.13 (17.601)
LSEQ at Week 1: Awake following sleep	(13) 5.85 (19.797)	(12) -12.08 (32.389)	(12) -2.04 (15.497)
LSEQ at Week 4: Awake following sleep	(12) 8.29 (16.218)	(8) -8.00 (43.825)	(12) -4.13 (19.931)
LSEQ at Week 8: Awake following sleep	(11) 7.23 (16.912)	(9) -10.72 (36.141)	(11) -7.55 (30.057)
LSEQ at Week 1: Behaviour following wakening	(13) 3.90 (12.435)	(12) -3.89 (32.063)	(12) -3.67 (7.671)
LSEQ at Week 4: Behaviour following wakening	(12) 1.03 (15.971)	(9) 5.78 (46.411)	(12) -9.89 (14.530)
LSEQ at Week 8: Behaviour following wakening	(11) -0.36 (13.725)	(9) 6.82 (49.170)	(11) -1.82 (19.954)
Change from Baseline, n (%)			
Clinic visit VRS score at Week 1			
Improved	8 (57.1)	9 (64.3)	9 (64.3)
No change	5 (35.7)	3 (21.4)	4 (28.6)
Worsened	1 (7.1)	2 (14.3)	1 (7.1)
Clinic visit VRS score at Week 4			
Improved	10 (76.9)	8 (80.0)	11 (78.6)
No change	3 (23.1)	2 (20.0)	2 (14.3)
Worsened	0	0	1 (7.1)
Clinic visit VRS score at Week 8			
Improved	9 (75.0)	9 (81.8)	9 (81.8)
No change	3 (25.0)	2 (18.2)	2 (18.2)
Worsened	0	0	0
Change from Week 4, (n) Mean (SD)			
Change from Week 4 in patient-recorded NRS score at Week 5	(13) -0.41 (1.409)	(10) -0.47 (1.989)	(14) -0.69 (0.991)
Change from Week 4 in patient-recorded NRS score at Week 6	(13) -0.46 (1.561)	(10) -0.83 (2.196)	(13) -0.69 (0.897)
Change from Week 4 in patient-recorded NRS score at Week 7	(12) 0.17 (1.972)	(10) 0.00 (3.604)	(12) -0.72 (1.127)
Change from Week 4 in patient-recorded NRS score at Week 8	(11) -0.42 (2.071)	(10) -0.33 (3.728)	(12) -0.92 (1.084)
Change from Week 4 in clinic visit VRS score at Week 8	(12) -0.08 (1.730)	(11) 0.36 (3.501)	(12) 0.08 (1.165)
Number of Subjects (%)			
EGFRI dose reduction	3 (18.8)	2 (14.3)	2 (14.3)

Withdrawal because of intense uncontrolled pruritus	0	0	0
EGFRI = epidermal growth factor receptor inhibitor: LSEQ = Leeds Sleep Evaluation Questionnaire; NRS = numerical rating scale; SD = standard deviation; VRS = verbal rating scale.			

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3
	2b	Specific objectives or hypotheses	3
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	3
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	4
Participants	4a	Eligibility criteria for participants	4
	4b	Settings and locations where the data were collected	4
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	4
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	4
	6b	Any changes to trial outcomes after the trial commenced, with reasons	Not applicable
Sample size	7a	How sample size was determined	4
	7b	When applicable, explanation of any interim analyses and stopping guidelines	Not applicable
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	4
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	4
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	4
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	4
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	3, 4

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	4
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	5
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	Not applicable
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	5, 6
	13b	For each group, losses and exclusions after randomisation, together with reasons	Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	4
	14b	Why the trial ended or was stopped	4
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	5, 6
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	6
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	6, 7, Supplemental Table 1
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Not applicable
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Not applicable
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	7
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	8
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	8
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	8
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	Not applicable
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	8

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

The neurokinin-1 antagonist orvepitant for EGFRI-induced pruritus in cancer patients: a randomised, placebo-controlled, phase II trial

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TITLE: The neurokinin-1 antagonist orvepitant for EGFRI-induced pruritus in cancer patients: a randomised, placebo-controlled, phase II trial

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ABSTRACT

Objective To evaluate the efficacy of orvepitant (10 or 30 mg given once daily, orally for 4 weeks), a neurokinin-1 receptor antagonist, compared with placebo in reducing the intensity of epidermal growth factor receptor inhibitor (EGFRI)-induced intense pruritus

Design Randomised, double-blind, placebo-controlled clinical trial

Setting 15 hospitals in Italy and 5 hospitals in the United Kingdom

Participants 44 patients aged ≥18 years receiving an EGFRI for a histologically confirmed malignant solid tumour and experiencing moderate or intense pruritus after EGFRI treatment

Intervention 30 mg or 10 mg orvepitant or placebo tablets once daily for 4 weeks (randomised 1:1:1)

Primary and secondary outcome measures The primary endpoint was change from Baseline in mean patient-recorded numerical rating scale (NRS) score (over the last 3 recordings) at Week 4. Secondary outcome measures were NRS score, verbal rating scale score, Skindex-16, and Leeds Sleep Evaluation Questionnaire at each study visit (Baseline, Weeks 1, 4, 8); rescue medication use; EGFRI dose reduction; and study withdrawal because of intense uncontrolled pruritus.

Results The trial was terminated early because of recruitment challenges; only 44 of the planned 90 patients were randomised. All patients were analysed for efficacy and safety. Mean NRS score change from Baseline to Week 4 was -2.78 (SD: 2.64) points in the 30 mg group, -3.04 (SD: 3.06) points in the 10 mg group, and -3.21 (SD: 1.77) points in the placebo group; the difference between orvepitant and placebo was not statistically significant. No safety signal was detected. Adverse events related to orvepitant (asthenia, dizziness, dry mouth, hyperhidrosis) were all of mild or moderate severity.

Conclusions Orvepitant was safe and well tolerated. No difference in NRS score between the orvepitant and placebo groups was observed at the Week 4 primary endpoint. A number of explanations for this outcome are possible.

Trial registration number EudraCT 2013-002763-25

KEY WORDS: pruritus, EGFR inhibitor, neurokinin-1 antagonist, orvepitant

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The RELIEVE 1 study was the first randomised, double-blind, placebo-controlled study of a neurokinin-1 antagonist for EGFRI-induced pruritus.
- The RELIEVE 1 study provided new insights into the course, itch characteristics, and possible mechanism of EGFRI-induced pruritus.
- The enrolment target was not reached because of recruitment problems in the target population.

INTRODUCTION

While targeted biological therapies have increased patient survival for several tumour types, they are linked with a variety of adverse events (AEs), particularly dermatological AEs, including acneiform rash, hair changes. mucositis, xerosis/fissures, paronychia, and pruritus. Epidermal growth factor receptor inhibitors (EGFRIs) specifically are associated with these dermatological AEs that can require dose modification or treatment interruptions and thus interfere with these potentially life-prolonging therapies.[1-5] Rash, xerosis, and pruritus have the greatest impact on patient quality of life.[5-7] Pruritus incidence reported in clinical trials of anti-EGFR monoclonal antibodies (mAbs) and small-molecule EGFRIs ranges from 8% to 69% depending on the agent involved.[8-9] EGFRI-induced pruritus may be underreported or incompletely reported in clinical studies.[10] In a survey of cancer patients and survivors, pruritus is common and debilitating.[11,12] Lacouture et al. reported that pruritus occurs in approximately half of all patients treated with EGFRIs.[4] Finally, in a review of interviews conducted with 100 patients taking mainly EGFR mAbs, 72% of patients reported experiencing pruritus.[13] A safe and effective cancer-supportive care therapy to ameliorate the itching burden these patients experience is urgently needed.

Neurokinin-1 (NK1) receptors are 7-transmembrane receptors with a preferred peptide agonist ligand of substance P (SP).[14] SP produced by peripheral skin sensory nerve fibres is thought to promote itching via activation of NK1 receptors on keratinocytes and mast cells causing local inflammatory and vasodilatory effects.[15] Interestingly, Gerber et al. reported that mast cells significantly accumulate in the lesional skin of patients treated with EGFRIs and suggested that the antipruritic activity of the NK1 receptor antagonist aprepitant in this population is achieved by blocking the activation of mast cell NK1 receptors by SP, thereby preventing the release of mast cell histamine and other proinflammatory/pruritogenic mediators.[16-18] Recently another receptor, the Mas-related G-protein coupled receptor member X2 (MrgprX2), has been shown to be activated in humans by SP, and this interaction may contribute additionally to the proinflammatory effects mediated by mast cell degranulation.[19] SP and the NK1 receptor are also widely expressed centrally and have a role in transmission of the peripheral itch signal via the spinal superficial dorsal horn to higher brain centres for processing.[20] In rodents scratching behaviour can be blocked by neurotoxic destruction of spinal NK1 receptor-expressing neurons,[21,22] and *Tac1* (the gene encoding SP)-expressing spinal neurons has also been linked to the promotion of scratching behaviour.[23] Intradermal injection of SP in humans causes pruritus, erythema, and oedema.[24-26] Scratching behaviour induced by intradermal injection of either SP or a NK1 agonist or topical administration of a hapten in animals can all be profoundly reduced by NK1 antagonist treatment, including both orvepitant and aprepitant.[27-30] These data suggest that the NK1 receptor system is involved in itch signalling and therefore blockade of these pathways with NK1 receptor antagonists represents a potentially promising therapy for pruritic conditions, including EGFRI-induced pruritus.[31,32]

Aprepitant (Emend®, formerly MK-869) is the first commercially available drug of a new class of NK1 receptor antagonists for the prevention of chemotherapy-induced and postoperative nausea and vomiting. It has been evaluated in numerous open-label clinical studies of patients suffering from treatment-refractory pruritus, including a large number of patients suffering with acute EGFRI-induced pruritus.[33-49] In these uncontrolled studies, aprepitant acted as a rapid and highly effective antipruritic medication that also significantly improved patients' quality of life, leading to advocacy for clinical assessment of aprepitant and other emerging NK1 receptor antagonists in patients receiving agents with a high risk of pruritus.[50]

Like aprepitant, orvepitant is an orally active, potent, brain-penetrant, and selective non-surmountable NK1 antagonist that blocks SP signalling.[51-53] These compounds are active in the well characterised NK1 receptor pharmacodynamic gerbil foot-tapping model, in preclinical models of anxiety,[51-54] and, as reported above, in the gerbil scratching behaviour model.[28,29] In humans both compounds have pharmacokinetic properties consistent with once-daily oral dosing sufficient to achieve therapeutic plasma exposures that have high levels of central NK1 receptor occupancy.[55,56] Thus, orvepitant would be expected to achieve antipruritic efficacy similar to that of aprepitant in patients suffering from intense itch as a result of EGFRI treatment. The RELIEVE 1 study evaluating

the efficacy and safety of orvepitant is the first randomised, double-blind, placebo-controlled study of an NK1 antagonist for EGFRI-induced pruritus.

METHODS

Patient and public involvement

The primary endpoint was a patient recorded outcome. There was no public involvement.

Study design and enrolment

The primary objective of this exploratory Phase 2, multicentre, randomised, double-blind, placebo-controlled clinical trial was to evaluate the efficacy of orvepitant compared with placebo in reducing the intensity of intense EGFRI-induced pruritus. Pruritus intensity was measured primarily by change from Baseline in patient-recorded numerical rating scale (NRS) score ranging from 0 (no itch) to 10 (worst itch imaginable) points. On the basis of an assumed between-patient standard deviation (SD) of 2 points,[8] 23 patients per treatment arm were required to provide 80% power for a 2-sided 5% significance level hypothesis test to achieve a significant result when the true difference is at least 2 points. It was thus planned to enrol 30 patients per arm (90 total). After 20 months of recruitment, this target was far from being reached, and a blinded analysis of data variance indicated that it was highly unlikely that a statistically robust assessment of benefit could be made even if enrolment were completed. The sponsor decided to terminate enrolment. However, the study data for all enrolled patients were analysed.

Patients and treatments

Patients were enrolled at 15 hospitals in Italy and 5 hospitals in the United Kingdom between 13 November 2013 and 11 May 2015. Key eligibility criteria were age 18 years and older, monotherapy with an EGFRI (including cetuximab, panitumumab, erlotinib, gefitinib, lapatinib, and afatinib) for a histologically confirmed malignant solid tumour, moderate or intense pruritus after treatment with the EGFRI (defined as the mean of between 2 and 7 daily patient-reported average pruritus intensity NRS scores initially ≥7 and subsequently changed in April 2014 to ≥5 to improve study recruitment), pruritus treatment within the previous 3 months, and no use of aprepitant or fosaprepitant in the previous 4 weeks. The investigators randomised eligible patients according to a central randomisation code generated by the sponsor using an interactive voice response system (IVRS). The patients were assigned in a 1:1:1 ratio to receive 30 mg orvepitant, 10 mg orvepitant, or placebo tablets once daily (in the evening before bedtime) for 4 weeks. Randomisation was stratified by investigational site; block size was 6. Placebo tablets were identical in appearance to orvepitant tablets.

Assessments

Patients were followed-up for 4 weeks after treatment was completed or discontinued. Patients reported their NRS scores daily using an IVRS between Baseline and Week 8. At each study visit (Baseline, Week 1, Week 4, Week 8) an NRS score and a verbal rating scale (VRS) score were recorded. The VRS score was assigned in response to the following questions: How intense was your pruritus during the past 24 hours? Did you have no pruritus, weak pruritus, moderate pruritus, severe pruritus, or very severe pruritus? Scores ranged from 0 (no pruritus) to 4 (very severe pruritus). Both the NRS and VRS are validated instruments for the measurement of pruritus intensity.[57] At each study visit, the patients also completed the Skindex-16 (an instrument to measure the effects of skin disease on health-related quality of life),[58] and the Leeds Sleep Evaluation Questionnaire (LSEQ; a 10-item instrument to assess changes in sleep quality over the course of an intervention). Safety was assessed by physical examination (including Eastern Cooperative Oncology Group [ECOG] status) and 12-lead electrocardiogram (ECG) at Baseline and Week 8, vital signs and laboratory tests (haematology, serum biochemistry, urinalysis) at each visit, and recording of AEs throughout the study. AEs were graded and categorised according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE). Use of concomitant medications, including

EGFRIs and any rescue medication, was recorded throughout the study. Sparse pharmacokinetic sampling was conducted to allow for exploratory analysis of the correlation of orvepitant plasma levels with clinical efficacy and secondary assessment scores.

Endpoints

The primary endpoint was change from Baseline in mean patient-recorded NRS score (over the last 3 recordings) at Week 4 for orvepitant 30 mg versus placebo. Secondary endpoints were also evaluated: change from Baseline in mean patient-recorded NRS score (last 3 recordings) each week; change from Baseline in mean patient-recorded NRS score (all values in the week) at Weeks 1, 4, 8; change from Baseline in patient-recorded NRS score at Days 2, 3, 4, 5, 6, 7, 8; change from Week 4 in patient-recorded NRS score (over the last 3 recordings) at Weeks 5, 6, 7, 8; change from Week 4 in VRS score at Week 8; change from Baseline in Skindex-16 quality of life at Weeks, 1, 4, 8; change from Baseline in LSEQ at Weeks, 1, 4, 8; rescue medication use; EGFRI dose reduction; and study withdrawal because of intense uncontrolled pruritus.

Statistical analysis

Efficacy endpoints were analysed in the intention-to-treat (ITT) population of all randomised patients who had received at least the first dose of study medication and had at least 1 post-treatment efficacy assessment. The primary endpoint was analysed by mixed-model repeated measures analysis with the primary inference being the change from Baseline in patient-reported NRS scores averaged across the last 3 values of the fourth week of dosing fitted as the response variable in the mixed model. The model included treatment group, study pooled site, study visit, the interaction between study visit and treatment group, the covariate (the baseline value of the variable being analysed) and the interaction between baseline covariate and visit. The 3 treatment groups were analysed together in one model. Point estimates and corresponding 95% confidence intervals were constructed for the difference between each dose of orvepitant and placebo for each week. The primary efficacy endpoint was tested at a 5% level of significance using a two-sided test to test orvepitant 30 mg versus placebo, and no adjustment for multiple comparisons was made for the patient-recorded NRS score orvepitant 10 mg versus placebo test or the secondary and exploratory endpoints. Safety was analysed in the safety population of all patients who received a dose of study medication using descriptive statistics.

RESULTS

Patients

A total of 44 patients were randomised and treated: 16 to orvepitant 30 mg, 14 to orvepitant 10 mg, and 14 to placebo. Nine patients discontinued the study (Figure 1). All patients were Caucasian, and 26 (59%) were male and 18 (41%) female. Median age was 68 years (range: 35 to 83 years), and 32 (73%) patients were aged 65 or older. Mean baseline NRS score ranged from 5.88 (SD: 0.93) in the placebo group to 6.68 (SD: 1.28) in the 30 mg orvepitant group. At Baseline, most patients had moderate to severe pruritus, and the most common locations were the head (specifically the scalp 26 [59%] patients) and the trunk (11 [25%]). Baseline assessments of acneiform rash and maculopapular rash showed a similar pattern (Table 1).

Table 1. Demographic and baseline characteristics

Characteristic	Orvepitant 30 mg *N* = 16	Orvepitant 10 mg *N* = 14	Placebo *N* = 14	Total *N* = 44
Age (years), median (range)	69.0 (43, 83)	73.5 (49, 81)	67.0 (35, 76)	68.0 (35, 83)
Age groups, n (%)				

< 65 years	4 (25.0)	4 (28.6)	4 (28.6)	12 (27.3)
≥ 65 years	12 (75.0)	10 (71.4)	10 (71.4)	32 (72.7)
Gender, n (%)				
Female	5 (31.3)	5 (35.7)	8 (57.1)	18 (40.9)
Male	11 (68.8)	9 (64.3)	6 (42.9)	26 (59.1)
Race, n (%)				
Caucasian	16 (100.0)	14 (100.0)	14 (100.0)	44 (100.0)
Time since cancer diagnosis (months), median (range)	17.5 (1, 131)	29.7 (12, 129)	20.8 (5, 60)	23.0 (1, 131)
Patient-reported NRS score				
Mean (SD)	6.68 (1.278)	6.95 (1.4.13)	5.88 (0.930)	NC
Median (range)	6.86 (4.8, 9.3)	7.00 (5.0, 10.0)	5.57 (5.0, 7.4)	NC
PRURITUS				
CTCAE grade, n (%)				
Grade 1	2 (12.5)	0	0	2 (4.5)
Grade 2	8 (50.0)	9 (64.3)	11 (78.6)	28 (63.6)
Grade 3	5 (31.3)	5 (35.7)	3 (21.4)	13 (29.5)
Unknown	1 (6.3)	0	0	1 (2.3)
Location, n (%)				
Head	8 (50.0)	6 (42.9)	12 (85.7)	26 (59.1)
Trunk	7 (43.8)	3 (21.4)	1 (7.1)	11 (25.0)
Arms	0	3 (21.4)	0	3 (6.8)
Legs	0	2 (14.3)	1 (7.1)	3 (6.8)
Unknown	1 (6.3)	0	0	1 (2.3)
ACNEIFORM RASH				
CTCAE grade, n (%)				
Grade 1	2 (12.5)	3 (21.4)	2 (14.3)	7 (15.9)
Grade 2	7 (43.8)	7 (50.0)	10 (71.4)	24 (54.5)
Grade 3	6 (37.5)	3 (21.4)	1 (7.1)	10 (22.7)
Unknown	1 (6.3)	1 (7.1)	1 (7.1)	3 (6.8)
Location, n (%)				
Head	7 (43.8)	5 (35.7)	11 (78.6)	23 (52.3)
Trunk	7 (43.8)	5 (35.7)	0	12 (27.3)
Arms	1 (6.3)	3 (21.4)	1 (7.1)	5 (11.4)
Legs	0	0	1 (7.1)	1 (2.3)
Unknown	1 (6.3)	1 (7.1)	1 (7.1)	3 (6.8)
MACULOPAPULAR RASH				
CTCAE grade, n (%)				
Grade 1	3 (18.8)	5 (35.7)	5 (35.7)	13 (29.5)
Grade 2	8 (50.0)	5 (35.7)	8 (57.1)	21 (47.7)
Grade 3	4 (25.0)	3 (21.4)	0	7 (15.9)
Unknown	1 (6.3)	1 (7.1)	1 (7.1)	3 (6.8)
Location, n (%)				
Head	7 (43.8)	5 (35.7)	12 (85.7)	24 (54.5)

Trunk	7 (43.8)	4 (28.6)	0	11 (25.0)
Arms	1 (6.3)	4 (28.6)	0	5 (11.4)
Legs	0	0	1 (7.1)	1 (2.3)
Unknown	1 (6.3)	1 (7.1)	1 (7.1)	3 (6.8)
CTCAE = Common Terminology Criteria for Adverse Events; NC = not calculated; NRS = numerical rating scale; SD = standard deviation.				

The median dose number was 28 (range: 1 to 35) in the 30 mg group, 28 (range: 1 to 35) in the 10 mg group, and 29 (range: 28 to 39) in the placebo group. Five (11%) patients (all in the orvepitant groups) took the study drug for 1 week or less; 18 (41%) patients took the study drug (orvepitant or placebo) for 1 to 4 weeks, and 21 (48%) took the study drug for >4 weeks (maximum: 39 days).

All 44 patients were included in the ITT and safety populations and analysed according to the randomised treatment.

Efficacy

Patient compliance with daily reporting of NRS score was high; mean compliance rate was 92%, and median compliance rate was 100%. At Week 4, 38 subjects remained in the study. NRS score decreased from Baseline to Week 4 in all 3 groups (Table 2). The difference between orvepitant and placebo was not, however, statistically significant (30 mg group: $P = 0.12$, 10 mg group: $P = 0.19$).

Table 2. Change from Baseline in patient-reported numerical reporting scale scores at Week 4

Statistic	Orvepitant 30 mg *N* = 16	Orvepitant 10 mg *N* = 14	Placebo *N* = 14
n	**13**	**11**	**14**
Mean (SD)	-2.78 (2.64)	-3.04 (3.06)	-3.21 (1.77)
Median	-2.75	-2.00	-2.50
Minimum, maximum	-6.3, 3.0	-8.3, 1.1	-6.3, 0.0
LSMEANS estimate (95% CI)	-2.40 (-3.54, -1.27)	-2.53 (-3.80, -1.27)	-3.70 (-4.88, -2.52)
LSMEANS standard error	0.56	0.62	0.58
Orvepitant vs placebo difference (95% CI)	1.30 (-0.35, 2.95)	1.17 (-0.62, 2.96)	
P value	0.120	0.194	
CI = confidence interval; LSMEANS = least-squares means; SD = standard deviation. Note: Analysis results from mixed-model repeated measures analysis (Week 1 to Week 4) of the 3 treatment groups analysed together in one model: Change from Baseline = Treatment + Pooled Site + Visit + Treatment*Visit + Baseline Results + Visit*Baseline Covariate Interaction			

Secondary NRS and VRS endpoints reflected the results for the primary endpoint (Supplemental Table 1). Change from Baseline in Skindex-16 and LSEQ score showed no difference between the treatment groups at any time point. Rescue medication use and EGFRI dose reduction both occurred in 7 (16%) patients (3 in the orvepitant 30 mg group and 2 each in the orvepitant 10 mg and placebo groups). No subjects withdrew from the study because of intense uncontrolled pruritus.

Analyses of pharmacokinetic data were not conducted because of the lack of efficacy observed.

Safety

No safety signal was detected. A total of 34 (77%) patients experienced a treatment-emergent AE, but no unexpected AEs were reported. Only 4 mild and moderate AEs were considered by investigators to be related to orvepitant (Table 3). AEs that occurred in >5% of patients were asthenia (8 [18%] patients), skin toxicity (7 [16%] patients; term reported by the investigators was skin toxicity, which for EGFRIs commonly includes reactions such as skin rash, skin dryness [xerosis], pruritus, paronychia, hair abnormality, mucositis, and increased, growth of the eyelashes or facial hair[59]), diarrhoea (4 [9%] patients), cough (3 [7%] patients), rash (3 [7%] patients; terms as reported by the investigators included worsening of rash; hands, ankle and face rash; and rash cutaneous), and anaemia (3 [7%] patients). These more common AEs occurred in similar rates in the active and placebo groups except for anaemia and rash, which occurred infrequently and only in patients who received orvepitant. There was no apparent relationship between incidence or severity of AEs and orvepitant dose. No serious AEs were reported.

Table 3. Drug-related adverse events

	Orvepitant 30 mg *N* = 16 n (%)	Orvepitant 10 mg *N* = 14 n (%)	Placebo *N* = 14 n (%)
Any drug-related AE	3 (18.8)	1 (7.1)	0
Mild AEs			
Asthenia	1 (6.3)	0	0
Dizziness	0	1 (7.1)	0
Dry mouth	1 (6.3)	0	0
Moderate AEs			
Hyperhidrosis	1 (6.3)	0	0

No clinically significant changes in laboratory results, vital signs, physical examination findings, ECOG status, or ECG parameters were related to orvepitant.

DISCUSSION

Strengths and limitations of the study

The RELIEVE 1 study was the first randomised, double-blind, placebo-controlled study of an NK1 receptor antagonist for EGFRI-induced pruritus. The enrolment target was not reached because of recruitment problems in the critically ill target population. A similar response was seen in both placebo and active groups, a result for which there are several possible explanations. Nonetheless, this randomised, controlled study provided insights into the course, itch characteristics, and possible mechanisms of EGFRI-induced pruritus that may inform future studies.

Interpretation of the results

Orvepitant appeared safe and well tolerated, and the findings in this study are consistent with the substantial safety database accumulated to date on this product in different populations. The safety profile exhibited allows further investigation of orvepitant in this or other indications, including a planned Phase 3 study in refractory or unexplained chronic cough following a successful Phase 2 study in this indication.[60]

The efficacy results were, however, inconclusive; no significant difference between the active groups and the placebo group was observed. Patients experienced a mean reduction in itching of approximately 3 NRS points in the

2 orvepitant groups and the placebo group. This outcome may, of course, have resulted from the premature termination of the study and the consequent substantially reduced sample size making it difficult to determine a treatment difference. However, given there was no indication of difference between the arms, then it seems unlikely even if the study had been fully recruited that a treatment effect would have been detected. This outcome stands in stark contrast to the observation studies conducted with the NK1 antagonist aprepitant.[33-49] For example, in a 1-week, open-label study in 45 patients experiencing mainly EGFRI-induced severe pruritus, aprepitant therapy resulted in median visual analogue scale itch scores falling from 8 at Baseline to 1 after 7 days in a refractory group resistant to standard anti-pruritus treatments and from 8 to 0 in a naive group ($p<0.0001$ in both groups).[8] In this trial 41 (91%) patients responded to aprepitant (i.e., had a >50% reduction in pruritus intensity), and pruritus recurred in only 6 (13%) patients. This difference is difficult to rationalise given that the pharmacology of orvepitant and aprepitant are so comparable and both can achieve exposures likely to be therapeutic in humans following oral dosing. However, one plausible explanation for the results in the RELIEVE 1 study is the placebo effect that is often seen in clinical trials with subjective endpoints such as pruritus intensity.[61] In this study, critically ill patients were receiving a modern antineoplastic therapy, and they may have had a particularly high expectation of the benefit of their EGFRI therapy in general and of orvepitant's ability to reduce pruritus and thereby improve their quality of life.

A further explanation for the RELIEVE 1 study results relates to the pathological mechanism underlying the itch in these patients. EGFRI-induced pruritus arises acutely within the first 2 weeks after initiation of the anticancer therapy[5] and cutaneous accumulation, and activation of dermal mast cells[16,17,62] may be the most important driver of the itch signalling in these patients. This acute course contrasts with that of chronic pruritus conditions (defined as being >6 weeks in duration),[63] which are now linked to the sensitisation of itch signalling pathways similar to chronic pain, such that patients may report spontaneous itch (alloknesis) or an enhanced itch to normal itch-evoking stimuli (hyperknesis).[32,64,65] NK1 antagonists have shown great promise in randomised, placebo-controlled clinical studies as treatments for chronic pruritus conditions in general[66,67] as well as specifically for prurigo nodularis,[68] atopic dermatitis-associated pruritus,[69] and psoriasis-associated pruritus.[70] Orvepitant has shown efficacy against chronic refractory cough, which has also been recognised as a neural hypersensitivity syndrome.[60] Thus, NK1 antagonists may lack efficacy in acute pruritic conditions driven by cutaneous mast cells, such as EGFRI-induced pruritus, whilst being effective in chronic pruritus conditions by addressing itch pathway sensitisation.

A final explanation is that the improvement in itch scores seen in the 2 orvepitant groups and the placebo group may be attributable to the natural course of pruritus over the weeks following the initiation of EGFRI treatment. It is now known that patterns of cutaneous toxicities with EGFRI treatment can vary with time; for example, the intensity of acneiform rash that is associated with pruritus rises and falls dramatically in the first month.[71] If this were the case for itch intensity, it would be difficult to show a benefit against such a dynamic and self-limiting background.

Implications for future studies

Recruitment for this study was stopped after 20 months when only 44 of the planned 90 subjects had been enrolled. Despite evidence in the literature of a high prevalence of EGFRI-induced pruritus,[1-11,13,50,72,73] we experienced substantial difficulty identifying patients with severe enough pruritus (i.e., NRS score ≥ 5) to enable detection of post-treatment change. Study enrolment may have been limited by the fact that all investigators were oncologists, who are faced with multiple AEs in patients receiving EGFRIs (e.g., diarrhoea, rash, asthenia, nausea and vomiting, conjunctivitis, mucositis) that may have taken precedence over pruritus, a purely subjective symptom that is not widely reported in the oncology community.[10] Patients may also have been unwilling to enter the study because pruritus is not a major priority for them compared to their cancer.

NK1 antagonists may still hold potential for treatment of skin toxicities experienced by cancer patients treated with EGFRIs or other targeted therapies. However, future studies will require a more complete understanding of the epidemiology and course of target cancer therapy-induced pruritus to enable appropriate selection and sizing of the

patient population to achieve statistical power and a design that minimises or quantifies the placebo effect. Furthermore, greater knowledge of the pathological mechanism underlying the pruritus in this condition is needed. Without these advances, the experience of this trial shows that further investigation of this particular drug-induced pruritus condition at the current juncture will prove challenging.

FIGURE LEGENDS

Figure 1. Disposition of RELIEVE 1 patients

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Data sharing statement The deidentified data set for this study is available upon reasonable request from the study sponsor NeRRe Therapeutics Ltd.

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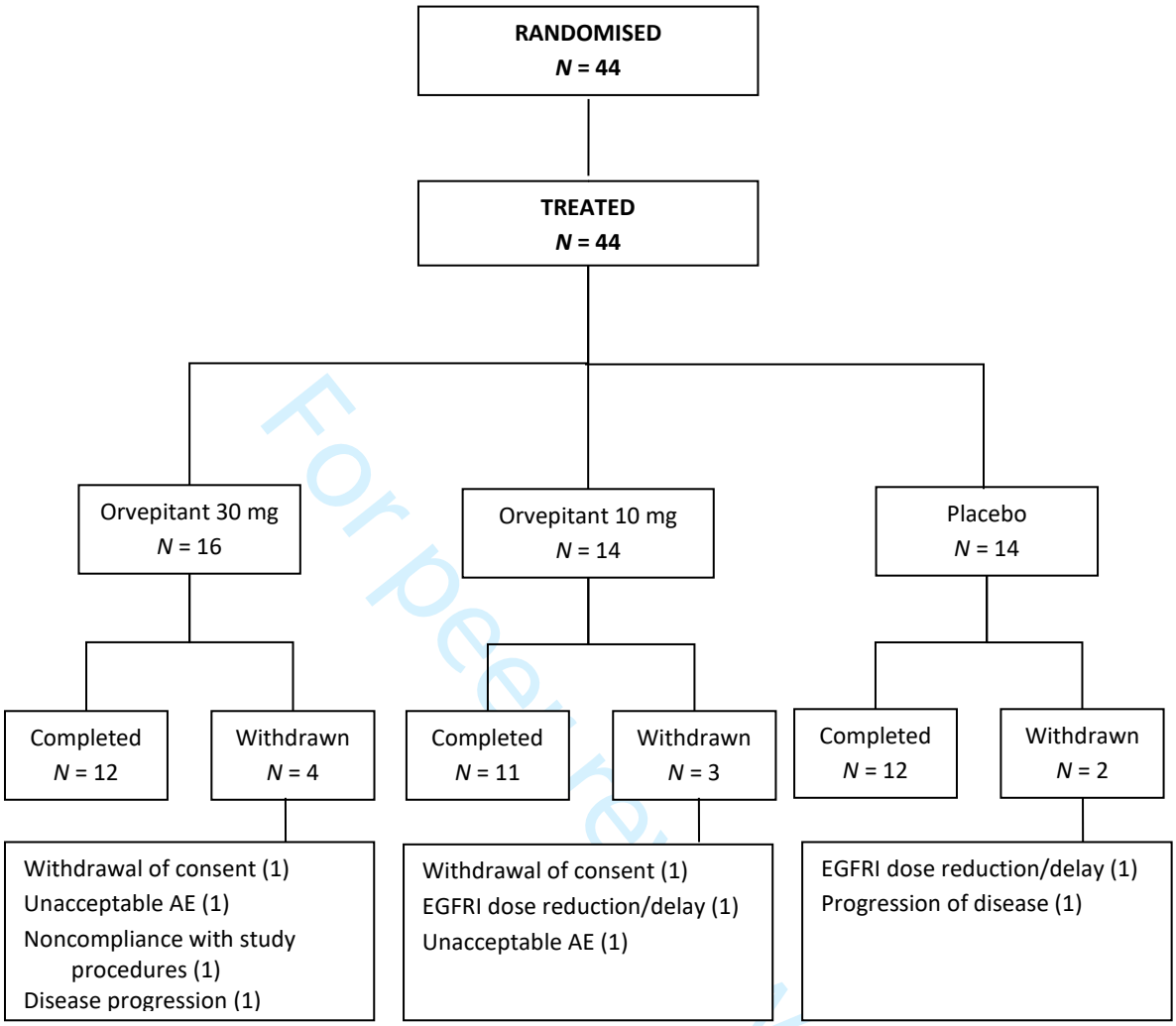

Supplemental Table 1. Summary of secondary efficacy endpoints

Statistic	Orvepitant 30 mg *N* = 16	Orvepitant 10 mg *N* = 14	Placebo *N* = 14
Change from Baseline, (n) Mean (SD)			
Patient-recorded NRS score (last 3 recordings) at Week 1	(16) -1.18 (1.55)	(13) -1.66 (2.48)	(14) -1.16 (1.41)
Patient-recorded NRS score (last 3 recordings) at Week 2	(14) -2.33 (2.00)	(13) -2.85 (3.43)	(13) -2.76 (1.96)
Patient-recorded NRS score (last 3 recordings) at Week 3	(14) -2.16 (2.56)	(11) -3.14 (2.77)	(14) -3.26 (2.00)
Patient-recorded NRS score (last 3 recordings) at Week 5	(13) -3.19 (2.88)	(10) -3.32 (3.19)	(14) -3.90 (2.19)
Patient-recorded NRS score (last 3 recordings) at Week 6	(13) -3.24 (2.89)	(10) -3.68 (2.55)	(13) -4.00 (1.78)
Patient-recorded NRS score (last 3 recordings) at Week 7	(12) -2.49 (2.91)	(10) -2.85 (2.52)	(12) -4.13 (2.33)
Patient-recorded NRS score (last 3 recordings) at Week 8	(11) -2.86 (2.91)	(10) -3.18 (2.68)	(12) -4.32 (2.27)
Patient-recorded NRS score (all week) at Week 1	(16) -0.96 (1.09)	(13) -1.34 (1.93)	(14) -0.86 (1.00)
Patient-recorded NRS score (all week) at Week 4	(13) -2.64 (2.61)	(11) -3.05 (3.00)	(14) -3.20 (1.96)
Patient-recorded NRS score (all week) at Week 8	(11) -2.65 (2.81)	(10) -3.15 (2.66)	(12) -4.29 (2.33)
Clinic-visit NRS score at Week 1	(14) -1.93 (1.73)	(14) -2.21 (3.19)	(14) -3.00 (2.60)
Clinic-visit NRS score at Week 4	(13) -3.38 (2.69)	(11) -4.27 (2.94)	(14) -4.14 (2.18)
Clinic-visit NRS score at Week 8	(13) -3.50 (2.71)	(11) -3.91 (2.66)	(12) -3.92 (2.35)
Patient-recorded NRS score at Day 2	(16) -0.61 (1.29)	(12) -0.84 (1.24)	(13) -0.33 (0.74)
Patient-recorded NRS score at Day 3	(14) -0.96 (0.99)	(11) -0.86 (1.64)	(13) -0.41 (0.65)
Patient-recorded NRS score at Day 4	(14) -0.85 (1.09)	(12) -1.04 (1.88)	(14) -0.81 (1.28)
Patient-recorded NRS score at Day 5	(13) -1.35 (1.12)	(12) -1.29 (2.23)	(13) -1.18 (1.45)
Patient-recorded NRS score at Day 6	(14) -1.28 (1.68)	(11) -1.31 (2.20)	(11) -1.30 (1.54)
Patient-recorded NRS score at Day 7	(14) -1.42 (2.30)	(12) -1.87 (3.63)	(13) -1.33 (1.89)
Patient-recorded NRS score at Day 8	(14) -1.85 (2.31)	(11) -1.83 (2.42)	(14) -1.88 (2.03)
Skindex-16 at Week 1: Symptoms	(14) -12.56 (22.25)	(13) 1.24 (25.05)	(13) -2.88 (18.50)
Skindex-16 at Week 4: Symptoms	(13) -8.29 (25.06)	(11) -9.09 (36.94)	(13) -7.69 (29.56)
Skindex-16 at Week 8: Symptoms	(12) -8.09 (23.60)	(11) -8.71 (36.19)	(12) -4.02 (33.30)
Skindex-16 at Week 1: Emotions	(14) -44.73 (16.35)	(13) -21.52 (27.80)	(13) -21.29 (18.20)
Skindex-16 at Week 4: Emotions	(13) -32.60 (24.96)	(11) -31.96 (36.34)	(13) -25.69 (26.54)
Skindex-16 at Week 8: Emotions	(12) -35.37 (30.88)	(11) -37.23 (28.13)	(12) -36.86 (26.32)
Skindex-16 at Week 1: Functioning	(14) -13.33 (16.69)	(13) -12.05 (29.08)	(13) -1.28 (13.51)
Skindex-16 at Week 4: Functioning	(13) 2.05 (26.51)	(11) -11.51 (36.07)	(13) -1.80 (20.40)
Skindex-16 at Week 8: Functioning	(12) -0.83 (28.04)	(11) -22.73 (25.64)	(12) -5.00 (16.17)
LSEQ at Week 1: Getting to sleep	(13) -12.08 (22.10)	(12) -9.82 (23.50)	(12) -6.45 (16.97)
LSEQ at Week 4: Getting to sleep	(12) -12.36 (19.61)	(9) 3.37 (23.64)	(12) -8.47 (18.19)
LSEQ at Week 8: Getting to sleep	(11) -4.57 (13.67)	(9) 2.04 (25.47)	(11) -7.06 (23.68)
LSEQ at Week 1: Quality of sleep	(13) -6.77 (26.98)	(12) -13.29 (33.39)	(12) -5.67 (15.39)
LSEQ at Week 4: Quality of sleep	(12) -6.46 (20.63)	(9) -8.61 (39.09)	(12) -9.13 (17.60)

LSEQ at Week 8: Quality of sleep	(11) -6.73 (21.81)	(9) -17.22 (34.00)	(11) -10.14 (26.73)
LSEQ at Week 1: Awake following sleep	(13) 5.85 (19.80)	(12) -12.08 (32.39)	(12) -2.04 (15.50)
LSEQ at Week 4: Awake following sleep	(12) 8.29 (16.22)	(8) -8.00 (43.83)	(12) -4.13 (19.93)
LSEQ at Week 8: Awake following sleep	(11) 7.23 (16.91)	(9) -10.72 (36.14)	(11) -7.55 (30.06)
LSEQ at Week 1: Behaviour following wakening	(13) 3.90 (12.44)	(12) -3.89 (32.06)	(12) -3.67 (7.67)
LSEQ at Week 4: Behaviour following wakening	(12) 1.03 (15.97)	(9) 5.78 (46.41)	(12) -9.89 (14.53)
LSEQ at Week 8: Behaviour following wakening	(11) -0.36 (13.73)	(9) 6.82 (49.17)	(11) -1.82 (19.95)
Change from Baseline, n (%)			
VRS score at Week 1			
Improved	8 (57.1)	9 (64.3)	9 (64.3)
No change	5 (35.7)	3 (21.4)	4 (28.6)
Worsened	1 (7.1)	2 (14.3)	1 (7.1)
VRS score at Week 4			
Improved	10 (76.9)	8 (80.0)	11 (78.6)
No change	3 (23.1)	2 (20.0)	2 (14.3)
Worsened	0	0	1 (7.1)
VRS score at Week 8			
Improved	9 (75.0)	9 (81.8)	9 (81.8)
No change	3 (25.0)	2 (18.2)	2 (18.2)
Worsened	0	0	0
Change from Week 4, (n) Mean (SD)			
Patient-recorded NRS score (last 3 recordings) at Week 5	(13) -0.41 (1.409)	(10) -0.47 (1.989)	(14) -0.69 (0.991)
Patient-recorded NRS score (last 3 recordings) at Week 6	(13) -0.46 (1.561)	(10) -0.83 (2.196)	(13) -0.69 (0.897)
Patient-recorded NRS score (last 3 recordings) at Week 7	(12) 0.17 (1.972)	(10) 0.00 (3.604)	(12) -0.72 (1.127)
Patient-recorded NRS score (last 3 recordings) at Week 8	(11) -0.42 (2.071)	(10) -0.33 (3.728)	(12) -0.92 (1.084)
VRS score at Week 8	(12) -0.08 (1.730)	(11) 0.36 (3.501)	(12) 0.08 (1.165)
Number of Subjects (%)			
Prescribed rescue medication	6 (37.5)	4 (28.6)	2 (14.3)
Used rescue medication	3 (18.8)	2 (14.3)	2 (14.3)
EGFRI dose reduction	3 (18.8)	2 (14.3)	2 (14.3)
Withdrawal because of intense uncontrolled pruritus	0	0	0

EGFRI = epidermal growth factor receptor inhibitor: LSEQ = Leeds Sleep Evaluation Questionnaire; NRS = numerical rating scale; SD = standard deviation; VRS = verbal rating scale.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3, 4
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	4
Participants	4a	Eligibility criteria for participants	4
	4b	Settings and locations where the data were collected	4
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	4
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	4, 5
	6b	Any changes to trial outcomes after the trial commenced, with reasons	Not applicable
Sample size	7a	How sample size was determined	4
	7b	When applicable, explanation of any interim analyses and stopping guidelines	Not applicable
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	4
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	4
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	4
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	4
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	4

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	4
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	5
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	Not applicable
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	5, 6
	13b	For each group, losses and exclusions after randomisation, together with reasons	Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	4
	14b	Why the trial ended or was stopped	8,9
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	5, 6
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	7
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	7, Supplemental Table 1
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Not applicable
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Not applicable
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	8
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	8
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	8, 9
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	8, 9
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	Not applicable
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	10

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

The neurokinin-1 antagonist orvepitant for EGFRI-induced pruritus in cancer patients: a randomised, placebo-controlled, phase II trial

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TITLE: The neurokinin-1 antagonist orvepitant for EGFRI-induced pruritus in cancer patients: a randomised, placebo-controlled, phase II trial

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ABSTRACT

Objective To evaluate the efficacy of orvepitant (10 or 30 mg given once daily, orally for 4 weeks), a neurokinin-1 receptor antagonist, compared with placebo in reducing the intensity of epidermal growth factor receptor inhibitor (EGFRI)-induced intense pruritus

Design Randomised, double-blind, placebo-controlled clinical trial

Setting 15 hospitals in Italy and 5 hospitals in the United Kingdom

Participants 44 patients aged ≥18 years receiving an EGFRI for a histologically confirmed malignant solid tumour and experiencing moderate or intense pruritus after EGFRI treatment

Intervention 30 mg or 10 mg orvepitant or placebo tablets once daily for 4 weeks (randomised 1:1:1)

Primary and secondary outcome measures The primary endpoint was change from Baseline in mean patient-recorded numerical rating scale (NRS) score (over the last 3 recordings) at Week 4. Secondary outcome measures were NRS score, verbal rating scale score, Skindex-16, and Leeds Sleep Evaluation Questionnaire at each study visit (Baseline, Weeks 1, 4, 8); rescue medication use; EGFRI dose reduction; and study withdrawal because of intense uncontrolled pruritus.

Results The trial was terminated early because of recruitment challenges; only 44 of the planned 90 patients were randomised. All patients were analysed for efficacy and safety. Mean NRS score change from Baseline to Week 4 was -2.78 (SD: 2.64) points in the 30 mg group, -3.04 (SD: 3.06) points in the 10 mg group, and -3.21 (SD: 1.77) points in the placebo group; the difference between orvepitant and placebo was not statistically significant. No safety signal was detected. Adverse events related to orvepitant (asthenia, dizziness, dry mouth, hyperhidrosis) were all of mild or moderate severity.

Conclusions Orvepitant was safe and well tolerated. No difference in NRS score between the orvepitant and placebo groups was observed at the Week 4 primary endpoint. A number of explanations for this outcome are possible.

Trial registration number EudraCT 2013-002763-25

KEY WORDS: pruritus, EGFR inhibitor, neurokinin-1 antagonist, orvepitant

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The RELIEVE 1 study was the first randomised, double-blind, placebo-controlled study of a neurokinin-1 antagonist for EGFRI-induced pruritus.
- Patients reported scores for the primary endpoint of reduction of itch intensity on a daily basis using an interactive voice response system.
- Effects on sleep and quality of life were also measured.
- Itch is a subjective symptom and thus susceptible to a placebo effect.
- The enrolment target was not reached because of recruitment problems in the target population.

INTRODUCTION

While targeted biological therapies have increased patient survival for several tumour types, they are linked with a variety of adverse events (AEs), particularly dermatological AEs, including acneiform rash, hair changes. mucositis, xerosis/fissures, paronychia, and pruritus. Epidermal growth factor receptor inhibitors (EGFRIs) specifically are associated with these dermatological AEs that can require dose modification or treatment interruptions and thus interfere with these potentially life-prolonging therapies.[1-5] Rash, xerosis, and pruritus have the greatest impact on patient quality of life.[5-7] Pruritus incidence reported in clinical trials of anti-EGFR monoclonal antibodies (mAbs) and small-molecule EGFRIs ranges from 8% to 69% depending on the agent involved.[8-9] EGFRI-induced pruritus may be underreported or incompletely reported in clinical studies.[10] In a survey of cancer patients and survivors, pruritus is common and debilitating.[11,12] Lacouture et al. reported that pruritus occurs in approximately half of all patients treated with EGFRIs.[4] Finally, in a review of interviews conducted with 100 patients taking mainly EGFR mAbs, 72% of patients reported experiencing pruritus.[13] A safe and effective cancer-supportive care therapy to ameliorate the itching burden these patients experience is urgently needed.

Neurokinin-1 (NK1) receptors are 7-transmembrane receptors with a preferred peptide agonist ligand of substance P (SP).[14] SP produced by peripheral skin sensory nerve fibres is thought to promote itching via activation of NK1 receptors on keratinocytes and mast cells causing local inflammatory and vasodilatory effects.[15] Interestingly, Gerber et al. reported that mast cells significantly accumulate in the lesional skin of patients treated with EGFRIs and suggested that the antipruritic activity of the NK1 receptor antagonist aprepitant in this population is achieved by blocking the activation of mast cell NK1 receptors by SP, thereby preventing the release of mast cell histamine and other proinflammatory/pruritogenic mediators.[16-18] Recently another receptor, the Mas-related G-protein coupled receptor member X2 (MrgprX2), has been shown to be activated in humans by SP, and this interaction may contribute additionally to the proinflammatory effects mediated by mast cell degranulation.[19] SP and the NK1 receptor are also widely expressed centrally and have a role in transmission of the peripheral itch signal via the spinal superficial dorsal horn to higher brain centres for processing.[20] In rodents scratching behaviour can be blocked by neurotoxic destruction of spinal NK1 receptor-expressing neurons,[21,22] and *Tac1* (the gene encoding SP)-expressing spinal neurons has also been linked to the promotion of scratching behaviour.[23] Intradermal injection of SP in humans causes pruritus, erythema, and oedema.[24-26] Scratching behaviour induced by intradermal injection of either SP or a NK1 agonist or topical administration of a hapten in animals can all be profoundly reduced by NK1 antagonist treatment, including both orvepitant and aprepitant.[27-30] These data suggest that the NK1 receptor system is involved in itch signalling and therefore blockade of these pathways with NK1 receptor antagonists represents a potentially promising therapy for pruritic conditions, including EGFRI-induced pruritus.[31,32]

Aprepitant (Emend®, formerly MK-869) is the first commercially available drug of a new class of NK1 receptor antagonists for the prevention of chemotherapy-induced and postoperative nausea and vomiting. It has been evaluated in numerous open-label clinical studies of patients suffering from treatment-refractory pruritus, including a large number of patients suffering with acute EGFRI-induced pruritus.[33-49] In these uncontrolled studies, aprepitant acted as a rapid and highly effective antipruritic medication that also significantly improved patients' quality of life, leading to advocacy for clinical assessment of aprepitant and other emerging NK1 receptor antagonists in patients receiving agents with a high risk of pruritus.[50]

Like aprepitant, orvepitant is an orally active, potent, brain-penetrant, and selective non-surmountable NK1 antagonist that blocks SP signalling.[51-53] These compounds are active in the well characterised NK1 receptor pharmacodynamic gerbil foot-tapping model, in preclinical models of anxiety,[51-54] and, as reported above, in the gerbil scratching behaviour model.[28,29] In humans both compounds have pharmacokinetic properties consistent with once-daily oral dosing sufficient to achieve therapeutic plasma exposures that have high levels of central NK1 receptor occupancy.[55,56] Thus, orvepitant would be expected to achieve antipruritic efficacy similar to that of aprepitant in patients suffering from intense itch as a result of EGFRI treatment. The RELIEVE 1 study evaluating

the efficacy and safety of orvepitant is the first randomised, double-blind, placebo-controlled study of an NK1 antagonist for EGFRI-induced pruritus.

METHODS

Patient and public involvement

There was no patient or public involvement in the planning of this trial.

Study design and enrolment

The primary objective of this exploratory Phase 2, multicentre, randomised, double-blind, placebo-controlled clinical trial was to evaluate the efficacy of orvepitant compared with placebo in reducing the intensity of intense EGFRI-induced pruritus. Pruritus intensity was measured primarily by change from Baseline in patient-recorded numerical rating scale (NRS) score ranging from 0 (no itch) to 10 (worst itch imaginable) points. On the basis of an assumed between-patient standard deviation (SD) of 2 points,[8] 23 patients per treatment arm were required to provide 80% power for a 2-sided 5% significance level hypothesis test to achieve a significant result when the true difference is at least 2 points. It was thus planned to enrol 30 patients per arm (90 total). After 20 months of recruitment, this target was far from being reached, and a blinded analysis of data variance showing between-patient SD of 2.6 points indicated that it was highly unlikely that a statistically robust assessment of benefit could be made even if enrolment were completed. The sponsor decided to terminate enrolment. However, the study data for all enrolled patients were analysed.

Patients and treatments

Patients were enrolled at 15 hospitals in Italy and 5 hospitals in the United Kingdom between 13 November 2013 and 11 May 2015. Key eligibility criteria were age 18 years and older, monotherapy with an EGFRI (including cetuximab, panitumumab, erlotinib, gefitinib, lapatinib, and afatinib) for a histologically confirmed malignant solid tumour, moderate or intense pruritus after treatment with the EGFRI (defined as the mean of between 2 and 7 daily patient-reported average pruritus intensity NRS scores initially ≥7 and subsequently changed in April 2014 to ≥5 to improve study recruitment), pruritus treatment within the previous 3 months, and no use of aprepitant or fosaprepitant in the previous 4 weeks. The investigators randomised eligible patients according to a central randomisation code generated by the sponsor using an interactive voice response system (IVRS). The patients were assigned in a 1:1:1 ratio to receive 30 mg orvepitant, 10 mg orvepitant, or placebo tablets once daily (in the evening before bedtime) for 4 weeks. Randomisation was stratified by investigational site; block size was 6. Placebo tablets were identical in appearance to orvepitant tablets.

Assessments

Patients were followed-up for 4 weeks after treatment was completed or discontinued. Patients reported their NRS scores daily using an IVRS between Baseline and Week 8. At each study visit (Baseline, Week 1, Week 4, Week 8) an NRS score and a verbal rating scale (VRS) score were recorded. The VRS score was assigned in response to the following questions: How intense was your pruritus during the past 24 hours? Did you have no pruritus, weak pruritus, moderate pruritus, severe pruritus, or very severe pruritus? Scores ranged from 0 (no pruritus) to 4 (very severe pruritus). Both the NRS and VRS are validated instruments for the measurement of pruritus intensity.[57] At each study visit, the patients also completed the Skindex-16 (an instrument to measure the effects of skin disease on health-related quality of life),[58] and the Leeds Sleep Evaluation Questionnaire (LSEQ; a 10-item instrument to assess changes in sleep quality over the course of an intervention). Safety was assessed by physical examination (including Eastern Cooperative Oncology Group [ECOG] status) and 12-lead electrocardiogram (ECG) at Baseline and Week 8, vital signs and laboratory tests (haematology, serum biochemistry, urinalysis) at each visit, and recording of AEs throughout the study. AEs were graded and categorised according to the National Cancer

Institute's Common Terminology Criteria for Adverse Events (CTCAE). Use of concomitant medications, including EGFRIs and any rescue medication, was recorded throughout the study. Sparse pharmacokinetic sampling was conducted to allow for exploratory analysis of the correlation of orvepitant plasma levels with clinical efficacy and secondary assessment scores.

Endpoints

The primary endpoint was change from Baseline in mean patient-recorded NRS score (over the last 3 recordings) at Week 4. Secondary endpoints were also evaluated: change from Baseline in mean patient-recorded NRS score (last 3 recordings) each week; change from Baseline in mean patient-recorded NRS score (all values in the week) at Weeks 1, 4, 8; change from Baseline in patient-recorded NRS score at Days 2, 3, 4, 5, 6, 7, 8; change from Week 4 in patient-recorded NRS score (over the last 3 recordings) at Weeks 5, 6, 7, 8; change from Week 4 in VRS score at Week 8; change from Baseline in Skindex-16 quality of life at Weeks, 1, 4, 8; change from Baseline in LSEQ at Weeks, 1, 4, 8; rescue medication use; EGFRI dose reduction; and study withdrawal because of intense uncontrolled pruritus.

Statistical analysis

Efficacy endpoints were analysed in the modified intention-to-treat (mITT) population of all randomised patients who had received at least the first dose of study medication and had at least 1 post-treatment efficacy assessment. The primary endpoint was analysed by mixed-model repeated measures analysis with the primary inference being the change from Baseline in patient-reported NRS scores averaged across the last 3 values of the fourth week of dosing fitted as the response variable in the mixed model. The model included treatment group, study pooled site, study visit, the interaction between study visit and treatment group, the covariate (the baseline value of the variable being analysed) and the interaction between baseline covariate and visit. The 3 treatment groups were analysed together in one model. Point estimates and corresponding 95% confidence intervals were constructed for the difference between each dose of orvepitant and placebo for each week. The primary efficacy endpoint was tested at a 5% level of significance using a two-sided test to test orvepitant 30 mg versus placebo, and no adjustment for multiple comparisons was made for the patient-recorded NRS score orvepitant 10 mg versus placebo test or the secondary and exploratory endpoints. Safety was analysed in the safety population of all patients who received a dose of study medication using descriptive statistics.

RESULTS

Patients

A total of 44 patients were randomised and treated: 16 to orvepitant 30 mg, 14 to orvepitant 10 mg, and 14 to placebo. Nine patients discontinued the study (Figure 1). All patients were Caucasian, and 26 (59%) were male and 18 (41%) female. Median age was 68 years (range: 35 to 83 years), and 32 (73%) patients were aged 65 or older. Mean baseline NRS score ranged from 5.88 (SD: 0.93) in the placebo group to 6.68 (SD: 1.28) in the 30 mg orvepitant group. At Baseline, most patients had moderate to severe pruritus, and the most common locations were the head (specifically the scalp 26 [59%] patients) and the trunk (11 [25%]). Baseline assessments of acneiform rash and maculopapular rash showed a similar pattern (Table 1).

Table 1. Demographic and baseline characteristics

Characteristic	Orvepitant 30 mg *N* = 16	Orvepitant 10 mg *N* = 14	Placebo *N* = 14	Total *N* = 44
Age (years), median (range)	69.0 (43, 83)	73.5 (49, 81)	67.0 (35, 76)	68.0 (35, 83)

Age groups, n (%)				
< 65 years	4 (25.0)	4 (28.6)	4 (28.6)	12 (27.3)
≥ 65 years	12 (75.0)	10 (71.4)	10 (71.4)	32 (72.7)
Gender, n (%)				
Female	5 (31.3)	5 (35.7)	8 (57.1)	18 (40.9)
Male	11 (68.8)	9 (64.3)	6 (42.9)	26 (59.1)
Race, n (%)				
Caucasian	16 (100.0)	14 (100.0)	14 (100.0)	44 (100.0)
Time since cancer diagnosis (months), median (range)	17.5 (1, 131)	29.7 (12, 129)	20.8 (5, 60)	23.0 (1, 131)
Patient-reported NRS score				
Mean (SD)	6.68 (1.278)	6.95 (1.4.13)	5.88 (0.930)	NC
Median (range)	6.86 (4.8, 9.3)	7.00 (5.0, 10.0)	5.57 (5.0, 7.4)	NC
PRURITUS				
CTCAE grade, n (%)				
Grade 1	2 (12.5)	0	0	2 (4.5)
Grade 2	8 (50.0)	9 (64.3)	11 (78.6)	28 (63.6)
Grade 3	5 (31.3)	5 (35.7)	3 (21.4)	13 (29.5)
Unknown	1 (6.3)	0	0	1 (2.3)
Location, n (%)				
Head	8 (50.0)	6 (42.9)	12 (85.7)	26 (59.1)
Trunk	7 (43.8)	3 (21.4)	1 (7.1)	11 (25.0)
Arms	0	3 (21.4)	0	3 (6.8)
Legs	0	2 (14.3)	1 (7.1)	3 (6.8)
Unknown	1 (6.3)	0	0	1 (2.3)
ACNEIFORM RASH				
CTCAE grade, n (%)				
Grade 1	2 (12.5)	3 (21.4)	2 (14.3)	7 (15.9)
Grade 2	7 (43.8)	7 (50.0)	10 (71.4)	24 (54.5)
Grade 3	6 (37.5)	3 (21.4)	1 (7.1)	10 (22.7)
Unknown	1 (6.3)	1 (7.1)	1 (7.1)	3 (6.8)
Location, n (%)				
Head	7 (43.8)	5 (35.7)	11 (78.6)	23 (52.3)
Trunk	7 (43.8)	5 (35.7)	0	12 (27.3)
Arms	1 (6.3)	3 (21.4)	1 (7.1)	5 (11.4)
Legs	0	0	1 (7.1)	1 (2.3)
Unknown	1 (6.3)	1 (7.1)	1 (7.1)	3 (6.8)
MACULOPAPULAR RASH				
CTCAE grade, n (%)				
Grade 1	3 (18.8)	5 (35.7)	5 (35.7)	13 (29.5)
Grade 2	8 (50.0)	5 (35.7)	8 (57.1)	21 (47.7)
Grade 3	4 (25.0)	3 (21.4)	0	7 (15.9)
Unknown	1 (6.3)	1 (7.1)	1 (7.1)	3 (6.8)
Location, n (%)				

Head	7 (43.8)	5 (35.7)	12 (85.7)	24 (54.5)
Trunk	7 (43.8)	4 (28.6)	0	11 (25.0)
Arms	1 (6.3)	4 (28.6)	0	5 (11.4)
Legs	0	0	1 (7.1)	1 (2.3)
Unknown	1 (6.3)	1 (7.1)	1 (7.1)	3 (6.8)
CTCAE = Common Terminology Criteria for Adverse Events; NC = not calculated; NRS = numerical rating scale; SD = standard deviation.				

The median dose number was 28 (range: 1 to 35) in the 30 mg group, 28 (range: 1 to 35) in the 10 mg group, and 29 (range: 28 to 39) in the placebo group. Five (11%) patients (all in the orvepitant groups) took the study drug for 1 week or less; 18 (41%) patients took the study drug (orvepitant or placebo) for 1 to 4 weeks, and 21 (48%) took the study drug for >4 weeks (maximum: 39 days).

All 44 patients were included in the mITT and safety populations and analysed according to the randomised treatment.

Efficacy

Patient compliance with daily reporting of NRS score was high; mean compliance rate was 92%, and median compliance rate was 100%. At Week 4, 38 subjects remained in the study. NRS score decreased from Baseline to Week 4 in all 3 groups (Table 2). The difference between orvepitant and placebo was not, however, statistically significant (30 mg group: $P = 0.12$, 10 mg group: $P = 0.19$).

Table 2. Change from Baseline in patient-reported numerical reporting scale scores at Week 4

Statistic	**Orvepitant 30 mg *N* = 16**	**Orvepitant 10 mg *N* = 14**	**Placebo *N* = 14**
n	**13**	**11**	**14**
Mean (SD)	-2.78 (2.64)	-3.04 (3.06)	-3.21 (1.77)
Median	-2.75	-2.00	-2.50
Minimum, maximum	-6.3, 3.0	-8.3, 1.1	-6.3, 0.0
LSMEANS estimate (95% CI)	-2.40 (-3.54, -1.27)	-2.53 (-3.80, -1.27)	-3.70 (-4.88, -2.52)
LSMEANS standard error	0.56	0.62	0.58
Orvepitant vs placebo difference (95% CI)	1.30 (-0.35, 2.95)	1.17 (-0.62, 2.96)	
P value	0.120	0.194	
CI = confidence interval; LSMEANS = least-squares means; SD = standard deviation. Note: Analysis results from mixed-model repeated measures analysis (Week 1 to Week 4) of the 3 treatment groups analysed together in one model: Change from Baseline = Treatment + Pooled Site + Visit + Treatment*Visit + Baseline Results + Visit*Baseline Covariate Interaction			

Secondary NRS and VRS endpoints reflected the results for the primary endpoint (Table 3). Change from Baseline in Skindex-16 and LSEQ score showed no difference between the treatment groups at any time point. Rescue medication use and EGFRI dose reduction both occurred in 7 (16%) patients (3 in the orvepitant 30 mg group and 2

each in the orvepitant 10 mg and placebo groups). No subjects withdrew from the study because of intense uncontrolled pruritus.

Table 3. Summary of secondary efficacy endpoints

Statistic	Orvepitant 30 mg *N* = 16	Orvepitant 10 mg *N* = 14	Placebo *N* = 14
Change from Baseline, (n) Mean (SD)			
Patient-recorded NRS score (last 3 recordings) at Week 1	(16) -1.18 (1.55)	(13) -1.66 (2.48)	(14) -1.16 (1.41)
Patient-recorded NRS score (last 3 recordings) at Week 2	(14) -2.33 (2.00)	(13) -2.85 (3.43)	(13) -2.76 (1.96)
Patient-recorded NRS score (last 3 recordings) at Week 3	(14) -2.16 (2.56)	(11) -3.14 (2.77)	(14) -3.26 (2.00)
Patient-recorded NRS score (last 3 recordings) at Week 5	(13) -3.19 (2.88)	(10) -3.32 (3.19)	(14) -3.90 (2.19)
Patient-recorded NRS score (last 3 recordings) at Week 6	(13) -3.24 (2.89)	(10) -3.68 (2.55)	(13) -4.00 (1.78)
Patient-recorded NRS score (last 3 recordings) at Week 7	(12) -2.49 (2.91)	(10) -2.85 (2.52)	(12) -4.13 (2.33)
Patient-recorded NRS score (last 3 recordings) at Week 8	(11) -2.86 (2.91)	(10) -3.18 (2.68)	(12) -4.32 (2.27)
Patient-recorded NRS score (all week) at Week 1	(16) -0.96 (1.09)	(13) -1.34 (1.93)	(14) -0.86 (1.00)
Patient-recorded NRS score (all week) at Week 4	(13) -2.64 (2.61)	(11) -3.05 (3.00)	(14) -3.20 (1.96)
Patient-recorded NRS score (all week) at Week 8	(11) -2.65 (2.81)	(10) -3.15 (2.66)	(12) -4.29 (2.33)
Clinic-visit NRS score at Week 1	(14) -1.93 (1.73)	(14) -2.21 (3.19)	(14) -3.00 (2.60)
Clinic-visit NRS score at Week 4	(13) -3.38 (2.69)	(11) -4.27 (2.94)	(14) -4.14 (2.18)
Clinic-visit NRS score at Week 8	(13) -3.50 (2.71)	(11) -3.91 (2.66)	(12) -3.92 (2.35)
Patient-recorded NRS score at Day 2	(16) -0.61 (1.29)	(12) -0.84 (1.24)	(13) -0.33 (0.74)
Patient-recorded NRS score at Day 3	(14) -0.96 (0.99)	(11) -0.86 (1.64)	(13) -0.41 (0.65)
Patient-recorded NRS score at Day 4	(14) -0.85 (1.09)	(12) -1.04 (1.88)	(14) -0.81 (1.28)
Patient-recorded NRS score at Day 5	(13) -1.35 (1.12)	(12) -1.29 (2.23)	(13) -1.18 (1.45)
Patient-recorded NRS score at Day 6	(14) -1.28 (1.68)	(11) -1.31 (2.20)	(11) -1.30 (1.54)
Patient-recorded NRS score at Day 7	(14) -1.42 (2.30)	(12) -1.87 (3.63)	(13) -1.33 (1.89)
Patient-recorded NRS score at Day 8	(14) -1.85 (2.31)	(11) -1.83 (2.42)	(14) -1.88 (2.03)
Skindex-16 at Week 1: Symptoms	(14) -12.56 (22.25)	(13) 1.24 (25.05)	(13) -2.88 (18.50)
Skindex-16 at Week 4: Symptoms	(13) -8.29 (25.06)	(11) -9.09 (36.94)	(13) -7.69 (29.56)
Skindex-16 at Week 8: Symptoms	(12) -8.09 (23.60)	(11) -8.71 (36.19)	(12) -4.02 (33.30)
Skindex-16 at Week 1: Emotions	(14) -44.73 (16.35)	(13) -21.52 (27.80)	(13) -21.29 (18.20)
Skindex-16 at Week 4: Emotions	(13) -32.60 (24.96)	(11) -31.96 (36.34)	(13) -25.69 (26.54)
Skindex-16 at Week 8: Emotions	(12) -35.37 (30.88)	(11) -37.23 (28.13)	(12) -36.86 (26.32)
Skindex-16 at Week 1: Functioning	(14) -13.33 (16.69)	(13) -12.05 (29.08)	(13) -1.28 (13.51)
Skindex-16 at Week 4: Functioning	(13) 2.05 (26.51)	(11) -11.51 (36.07)	(13) -1.80 (20.40)
Skindex-16 at Week 8: Functioning	(12) -0.83 (28.04)	(11) -22.73 (25.64)	(12) -5.00 (16.17)
LSEQ at Week 1: Getting to sleep	(13) -12.08 (22.10)	(12) -9.82 (23.50)	(12) -6.45 (16.97)
LSEQ at Week 4: Getting to sleep	(12) -12.36 (19.61)	(9) 3.37 (23.64)	(12) -8.47 (18.19)

LSEQ at Week 8: Getting to sleep	(11) -4.57 (13.67)	(9) 2.04 (25.47)	(11) -7.06 (23.68)
LSEQ at Week 1: Quality of sleep	(13) -6.77 (26.98)	(12) -13.29 (33.39)	(12) -5.67 (15.39)
LSEQ at Week 4: Quality of sleep	(12) -6.46 (20.63)	(9) -8.61 (39.09)	(12) -9.13 (17.60)
LSEQ at Week 8: Quality of sleep	(11) -6.73 (21.81)	(9) -17.22 (34.00)	(11) -10.14 (26.73)
LSEQ at Week 1: Awake following sleep	(13) 5.85 (19.80)	(12) -12.08 (32.39)	(12) -2.04 (15.50)
LSEQ at Week 4: Awake following sleep	(12) 8.29 (16.22)	(8) -8.00 (43.83)	(12) -4.13 (19.93)
LSEQ at Week 8: Awake following sleep	(11) 7.23 (16.91)	(9) -10.72 (36.14)	(11) -7.55 (30.06)
LSEQ at Week 1: Behaviour following wakening	(13) 3.90 (12.44)	(12) -3.89 (32.06)	(12) -3.67 (7.67)
LSEQ at Week 4: Behaviour following wakening	(12) 1.03 (15.97)	(9) 5.78 (46.41)	(12) -9.89 (14.53)
LSEQ at Week 8: Behaviour following wakening	(11) -0.36 (13.73)	(9) 6.82 (49.17)	(11) -1.82 (19.95)
Change from Baseline, n (%)			
VRS score at Week 1			
Improved	8 (57.1)	9 (64.3)	9 (64.3)
No change	5 (35.7)	3 (21.4)	4 (28.6)
Worsened	1 (7.1)	2 (14.3)	1 (7.1)
VRS score at Week 4			
Improved	10 (76.9)	8 (80.0)	11 (78.6)
No change	3 (23.1)	2 (20.0)	2 (14.3)
Worsened	0	0	1 (7.1)
VRS score at Week 8			
Improved	9 (75.0)	9 (81.8)	9 (81.8)
No change	3 (25.0)	2 (18.2)	2 (18.2)
Worsened	0	0	0
Change from Week 4, (n) Mean (SD)			
Patient-recorded NRS score (last 3 recordings) at Week 5	(13) -0.41 (1.409)	(10) -0.47 (1.989)	(14) -0.69 (0.991)
Patient-recorded NRS score (last 3 recordings) at Week 6	(13) -0.46 (1.561)	(10) -0.83 (2.196)	(13) -0.69 (0.897)
Patient-recorded NRS score (last 3 recordings) at Week 7	(12) 0.17 (1.972)	(10) 0.00 (3.604)	(12) -0.72 (1.127)
Patient-recorded NRS score (last 3 recordings) at Week 8	(11) -0.42 (2.071)	(10) -0.33 (3.728)	(12) -0.92 (1.084)
VRS score at Week 8	(12) -0.08 (1.730)	(11) 0.36 (3.501)	(12) 0.08 (1.165)
Number of Subjects (%)			
Prescribed rescue medication	6 (37.5)	4 (28.6)	2 (14.3)
Used rescue medication	3 (18.8)	2 (14.3)	2 (14.3)
EGFRI dose reduction	3 (18.8)	2 (14.3)	2 (14.3)
Withdrawal because of intense uncontrolled pruritus	0	0	0
EGFRI = epidermal growth factor receptor inhibitor: LSEQ = Leeds Sleep Evaluation Questionnaire; NRS = numerical rating scale; SD = standard deviation; VRS = verbal rating scale.			

Analyses of pharmacokinetic data were not conducted because of the lack of efficacy observed.

Safety

No safety signal was detected. A total of 34 (77%) patients experienced a treatment-emergent AE, but no unexpected AEs were reported. Only 4 mild and moderate AEs were considered by investigators to be related to orvepitant (Table 4). AEs that occurred in >5% of patients were asthenia (8 [18%] patients), skin toxicity (7 [16%]

patients; term reported by the investigators was skin toxicity, which for EGFRIs commonly includes reactions such as skin rash, skin dryness [xerosis], pruritus, paronychia, hair abnormality, mucositis, and increased, growth of the eyelashes or facial hair[59]), diarrhoea (4 [9%] patients), cough (3 [7%] patients), rash (3 [7%] patients; terms as reported by the investigators included worsening of rash; hands, ankle and face rash; and rash cutaneous), and anaemia (3 [7%] patients). These more common AEs occurred in similar rates in the active and placebo groups except for anaemia and rash, which occurred infrequently and only in patients who received orvepitant. There was no apparent relationship between incidence or severity of AEs and orvepitant dose. No serious AEs were reported.

Table 4. Drug-related adverse events

	Orvepitant 30 mg *N* = 16 n (%)	**Orvepitant 10 mg *N* = 14 n (%)**	**Placebo *N* = 14 n (%)**
Any drug-related AE	3 (18.8)	1 (7.1)	0
Mild AEs			
Asthenia	1 (6.3)	0	0
Dizziness	0	1 (7.1)	0
Dry mouth	1 (6.3)	0	0
Moderate AEs			
Hyperhidrosis	1 (6.3)	0	0

No clinically significant changes in laboratory results, vital signs, physical examination findings, ECOG status, or ECG parameters were related to orvepitant.

DISCUSSION

Strengths and limitations of the study

The RELIEVE 1 study was the first randomised, double-blind, placebo-controlled study of an NK1 receptor antagonist for EGFRI-induced pruritus. The enrolment target was not reached because of recruitment problems in the critically ill target population. A similar response was seen in both placebo and active groups, a result for which there are several possible explanations. Nonetheless, this randomised, controlled study provided insights into the course, itch characteristics, and possible mechanisms of EGFRI-induced pruritus that may inform future studies.

Interpretation of the results

Orvepitant appeared safe and well tolerated, and the findings in this study are consistent with the substantial safety database accumulated to date on this product in different populations. The safety profile exhibited allows further investigation of orvepitant in this or other indications, including a planned Phase 3 study in refractory or unexplained chronic cough following a successful Phase 2 study in this indication.[60]

The efficacy results were, however, inconclusive; no significant difference between the active groups and the placebo group was observed. Patients experienced a mean reduction in itching of approximately 3 NRS points in the 2 orvepitant groups and the placebo group. This outcome may, of course, have resulted from the premature termination of the study and the consequent substantially reduced sample size making it difficult to determine a treatment difference. However, given there was no indication of difference between the arms, it seems unlikely even if the study had been fully recruited that a treatment effect would have been detected. This outcome stands in stark contrast to the observation studies conducted with the NK1 antagonist aprepitant.[33-49] For example, in a 1-week, open-label study in 45 patients experiencing mainly EGFRI-induced severe pruritus, aprepitant therapy resulted in

median visual analogue scale itch scores falling from 8 at Baseline to 1 after 7 days in a refractory group resistant to standard anti-pruritus treatments and from 8 to 0 in a naive group ($p<0.0001$ in both groups).[8] In this trial 41 (91%) patients responded to aprepitant (i.e., had a >50% reduction in pruritus intensity), and pruritus recurred in only 6 (13%) patients. This difference is difficult to rationalise given that the pharmacology of orvepitant and aprepitant are so comparable and both can achieve exposures likely to be therapeutic in humans following oral dosing. However, one plausible explanation for the results in the RELIEVE 1 study is the placebo effect that is often seen in clinical trials with subjective endpoints such as pruritus intensity.[61] In this study, critically ill patients were receiving a modern antineoplastic therapy, and they may have had a particularly high expectation of the benefit of their EGFRI therapy in general and of orvepitant's ability to reduce pruritus and thereby improve their quality of life.

A further explanation for the RELIEVE 1 study results relates to the pathological mechanism underlying the itch in these patients. EGFRI-induced pruritus arises acutely within the first 2 weeks after initiation of the anticancer therapy[5] and cutaneous accumulation, and activation of dermal mast cells[16,17,62] may be the most important driver of the itch signalling in these patients. This acute course contrasts with that of chronic pruritus conditions (defined as being >6 weeks in duration),[63] which are now linked to the sensitisation of itch signalling pathways similar to chronic pain, such that patients may report spontaneous itch (alloknesis) or an enhanced itch to normal itch-evoking stimuli (hyperknesis).[32,64,65] NK1 antagonists have shown great promise in randomised, placebo-controlled clinical studies as treatments for chronic pruritus conditions in general[66,67] as well as specifically for prurigo nodularis,[68] atopic dermatitis-associated pruritus,[69] and psoriasis-associated pruritus.[70] Orvepitant has shown efficacy against chronic refractory cough, which has also been recognised as a neural hypersensitivity syndrome.[60] Thus, NK1 antagonists may lack efficacy in acute pruritic conditions driven by cutaneous mast cells, such as EGFRI-induced pruritus, whilst being effective in chronic pruritus conditions by addressing itch pathway sensitisation.

A final explanation is that the improvement in itch scores seen in the 2 orvepitant groups and the placebo group may be attributable to the natural course of pruritus over the weeks following the initiation of EGFRI treatment. It is now known that patterns of cutaneous toxicities with EGFRI treatment can vary with time; for example, the intensity of acneiform rash that is associated with pruritus rises and falls dramatically in the first month.[71] If this were the case for itch intensity, it would be difficult to show a benefit against such a dynamic and self-limiting background.

Implications for future studies

Recruitment for this study was stopped after 20 months when only 44 of the planned 90 subjects had been enrolled. Despite evidence in the literature of a high prevalence of EGFRI-induced pruritus,[1-11,13,50,72,73] we experienced substantial difficulty identifying patients with severe enough pruritus (i.e., NRS score ≥ 5) to enable detection of post-treatment change. Study enrolment may have been limited by the fact that all investigators were oncologists, who are faced with multiple AEs in patients receiving EGFRIs (e.g., diarrhoea, rash, asthenia, nausea and vomiting, conjunctivitis, mucositis) that may have taken precedence over pruritus, a purely subjective symptom that is not widely reported in the oncology community.[10] Patients may also have been unwilling to enter the study because pruritus is not a major priority for them compared to their cancer.

NK1 antagonists may still hold potential for treatment of skin toxicities experienced by cancer patients treated with EGFRIs or other targeted therapies. However, future studies will require a more complete understanding of the epidemiology and course of target cancer therapy-induced pruritus to enable appropriate selection and sizing of the patient population to achieve statistical power and a design that minimises or quantifies the placebo effect. Furthermore, greater knowledge of the pathological mechanism underlying the pruritus in this condition is needed. Without these advances, the experience of this trial shows that further investigation of this particular drug-induced pruritus condition at the current juncture will prove challenging.

FIGURE LEGENDS

Figure 1. Disposition of RELIEVE 1 patients

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Competing interests MT is a current employee and ER is a past employee of NeRRe Therapeutics Ltd, and both are inventors on a granted patent on novel uses of orvepitant. BV and PG received payment from NeRRe as investigators in this study. AD received payment from NeRRe for service as the Chief Medical Officer for this study. DJ is an employee of Cromsource, which received payment from NeRRe for statistical analysis of this study. PH has received payment from NeRRe as a consultant. ML reports receiving personal fees from Legacy Healthcare Services, AdgeroBio Pharmaceuticals, Amryt Pharma, Celldex Therapeutics, Debiopharm, Galderma Research and Development, Johnson & Johnson, Novocure, Lindi Skin, Merck Sharp and Dohme Corporation, Helsinn Healthcare SA, Janssen Research & Development LLC, Menlo Therapeutics, Novartis Pharmaceuticals Corporation, F. Hoffmann-La Roche AG, Abbvie Inc. Boehringer Ingelheim Pharma Gmbh & Co. KG, Allergan Inc, Amgen Inc, E.R. Squibb & Sons L.L.C., EMD Serono Inc, AstraZeneca Pharmaceuticals LP, Genentech Inc, Leo Pharma Inc, Seattle Genetics, Bayer, Männer SAS, Lutris Pharma, Pierre Fabre, Paxman Cooler Ltd, Adjucare, Dignitana, Biotechspert, Teva Pharmaceuticals Mexico, Parexel, OnQuality Pharmaceuticals Ltd, Novartis, Our Brain Bank, Millenium Pharmaceuticals and research funding from Berg Health, Bristol-Myers Squibb, Lutris Pharma, Novocure, Paxman, Biotest, and Veloce BioPharma. GT reports no conflicts of interest. AW reports receiving payment from NeRRe as Chair of the Advisory Board and from Advent Life Sciences for consultancy, Canbex Therapeutics as a nonexecutive director (past position), Calcico Therapeutics as chairman (past position) and a nonexecutive director (past position), and the Wellcome Trust as a member of grant committees. SS reports receiving payment from NeRRe as a member of the advisory board and from Almirall, Astellas Pharma, Beiersdorf, Celgene Corporation, Chugai Pharma, Creabilis, Daiichi Sankyo, Galderma, Helsinn, Kiniska Pharmaceuticals, Kneipp, Maruho Co, Merz Pharma, Novartis, Pierre Fabre Laboratories, Sienna Biopharmaceuticals, and Ziarco as a member of their advisory boards and from Menlo Therapeutics as an investigator and participation as an investigator in trials sponsored by Dermascence, Trevi Therapeutics, and Vanda Pharmaceuticals.

Patient consent All patients provided written informed consent for participation before enrolment in the trial.

Ethics approval This trial was approved by Ethics Committees for all investigational sites.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The deidentified data set for this study is available upon reasonable request from the study sponsor NeRRe Therapeutics Ltd.

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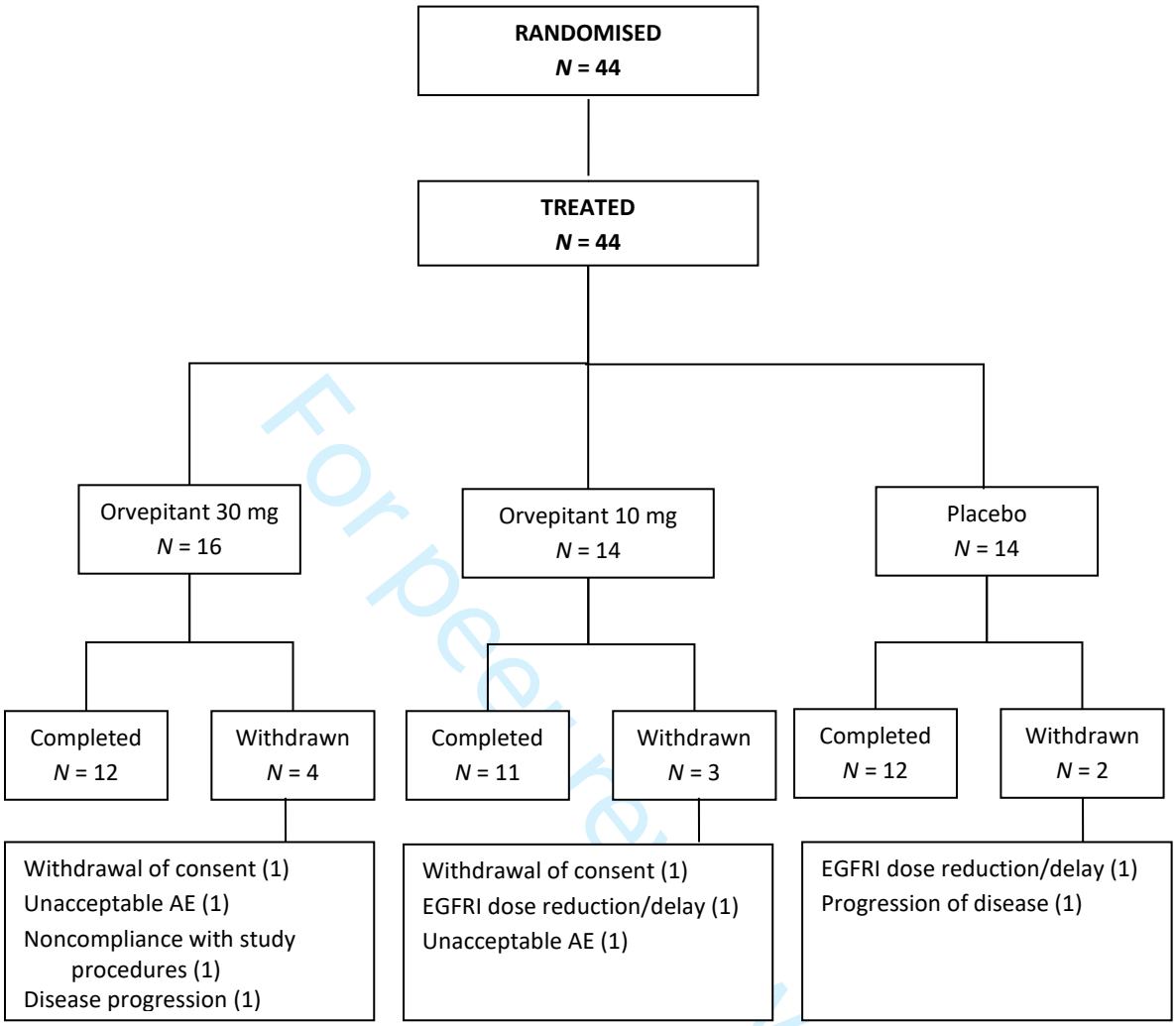

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3, 4
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	4
Participants	4a	Eligibility criteria for participants	4
	4b	Settings and locations where the data were collected	4
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	4
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	4, 5
	6b	Any changes to trial outcomes after the trial commenced, with reasons	Not applicable
Sample size	7a	How sample size was determined	4
	7b	When applicable, explanation of any interim analyses and stopping guidelines	Not applicable
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	4
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	4
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	4
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	4

Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	4
	11b	If relevant, description of the similarity of interventions	4
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	5
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	Not applicable
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	5, 6
	13b	For each group, losses and exclusions after randomisation, together with reasons	Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	4
	14b	Why the trial ended or was stopped	8,9
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	5, 6
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	7
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	7, 8 and 9
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Not applicable
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Not applicable
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	8
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	8
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	8, 9
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	8, 9
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	Not applicable
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	10

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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The neurokinin-1 antagonist orvepitant for EGFRI-induced pruritus in cancer patients: a randomised, placebo-controlled, phase II trial

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TITLE: The neurokinin-1 antagonist orvepitant for EGFRI-induced pruritus in cancer patients: a randomised, placebo-controlled, phase II trial

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ABSTRACT

Objective To evaluate the efficacy of orvepitant (10 or 30 mg given once daily, orally for 4 weeks), a neurokinin-1 receptor antagonist, compared with placebo in reducing the intensity of epidermal growth factor receptor inhibitor (EGFRI)-induced intense pruritus

Design Randomised, double-blind, placebo-controlled clinical trial

Setting 15 hospitals in Italy and 5 hospitals in the United Kingdom

Participants 44 patients aged ≥18 years receiving an EGFRI for a histologically confirmed malignant solid tumour and experiencing moderate or intense pruritus after EGFRI treatment

Intervention 30 mg or 10 mg orvepitant or placebo tablets once daily for 4 weeks (randomised 1:1:1)

Primary and secondary outcome measures The primary endpoint was change from Baseline in mean patient-recorded numerical rating scale (NRS) score (over the last 3 recordings) at Week 4. Secondary outcome measures were NRS score, verbal rating scale score, Skindex-16, and Leeds Sleep Evaluation Questionnaire at each study visit (Baseline, Weeks 1, 4, 8); rescue medication use; EGFRI dose reduction; and study withdrawal because of intense uncontrolled pruritus.

Results The trial was terminated early because of recruitment challenges; only 44 of the planned 90 patients were randomised. All patients were analysed for efficacy and safety. Mean NRS score change from Baseline to Week 4 was -2.78 (SD: 2.64) points in the 30 mg group, -3.04 (SD: 3.06) points in the 10 mg group, and -3.21 (SD: 1.77) points in the placebo group; the difference between orvepitant and placebo was not statistically significant. No safety signal was detected. Adverse events related to orvepitant (asthenia, dizziness, dry mouth, hyperhidrosis) were all of mild or moderate severity.

Conclusions Orvepitant was safe and well tolerated. No difference in NRS score between the orvepitant and placebo groups was observed at the Week 4 primary endpoint. A number of explanations for this outcome are possible.

Trial registration number EudraCT 2013-002763-25

KEY WORDS: pruritus, EGFR inhibitor, neurokinin-1 antagonist, orvepitant

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The RELIEVE 1 study was the first randomised, double-blind, placebo-controlled study of a neurokinin-1 antagonist for EGFRI-induced pruritus.
- Patients reported scores for the primary endpoint of reduction of itch intensity on a daily basis using an interactive voice response system.
- Effects on sleep and quality of life were also measured.
- Itch is a subjective symptom and thus susceptible to a placebo effect.
- The enrolment target was not reached because of recruitment problems in the target population.

INTRODUCTION

While targeted biological therapies have increased patient survival for several tumour types, they are linked with a variety of adverse events (AEs), particularly dermatological AEs, including acneiform rash, hair changes. mucositis, xerosis/fissures, paronychia, and pruritus. Epidermal growth factor receptor inhibitors (EGFRIs) specifically are associated with these dermatological AEs that can require dose modification or treatment interruptions and thus interfere with these potentially life-prolonging therapies.[1-5] Rash, xerosis, and pruritus have the greatest impact on patient quality of life.[5-7] Pruritus incidence reported in clinical trials of anti-EGFR monoclonal antibodies (mAbs) and small-molecule EGFRIs ranges from 8% to 69% depending on the agent involved.[8-9] EGFRI-induced pruritus may be underreported or incompletely reported in clinical studies.[10] In a survey of cancer patients and survivors, pruritus is common and debilitating.[11,12] Lacouture et al. reported that pruritus occurs in approximately half of all patients treated with EGFRIs.[4] Finally, in a review of interviews conducted with 100 patients taking mainly EGFR mAbs, 72% of patients reported experiencing pruritus.[13] A safe and effective cancer-supportive care therapy to ameliorate the itching burden these patients experience is urgently needed.

Neurokinin-1 (NK1) receptors are 7-transmembrane receptors with a preferred peptide agonist ligand of substance P (SP).[14] SP produced by peripheral skin sensory nerve fibres is thought to promote itching via activation of NK1 receptors on keratinocytes and mast cells causing local inflammatory and vasodilatory effects.[15] Interestingly, Gerber et al. reported that mast cells significantly accumulate in the lesional skin of patients treated with EGFRIs and suggested that the antipruritic activity of the NK1 receptor antagonist aprepitant in this population is achieved by blocking the activation of mast cell NK1 receptors by SP, thereby preventing the release of mast cell histamine and other proinflammatory/pruritogenic mediators.[16-18] Recently another receptor, the Mas-related G-protein coupled receptor member X2 (MrgprX2), has been shown to be activated in humans by SP, and this interaction may contribute additionally to the proinflammatory effects mediated by mast cell degranulation.[19] SP and the NK1 receptor are also widely expressed centrally and have a role in transmission of the peripheral itch signal via the spinal superficial dorsal horn to higher brain centres for processing.[20] In rodents scratching behaviour can be blocked by neurotoxic destruction of spinal NK1 receptor-expressing neurons,[21,22] and *Tac1* (the gene encoding SP)-expressing spinal neurons has also been linked to the promotion of scratching behaviour.[23] Intradermal injection of SP in humans causes pruritus, erythema, and oedema.[24-26] Scratching behaviour induced by intradermal injection of either SP or a NK1 agonist or topical administration of a hapten in animals can all be profoundly reduced by NK1 antagonist treatment, including both orvepitant and aprepitant.[27-30] These data suggest that the NK1 receptor system is involved in itch signalling and therefore blockade of these pathways with NK1 receptor antagonists represents a potentially promising therapy for pruritic conditions, including EGFRI-induced pruritus.[31,32]

Aprepitant (Emend®, formerly MK-869) is the first commercially available drug of a new class of NK1 receptor antagonists for the prevention of chemotherapy-induced and postoperative nausea and vomiting. It has been evaluated in numerous open-label clinical studies of patients suffering from treatment-refractory pruritus, including a large number of patients suffering with acute EGFRI-induced pruritus.[33-49] In these uncontrolled studies, aprepitant acted as a rapid and highly effective antipruritic medication that also significantly improved patients' quality of life, leading to advocacy for clinical assessment of aprepitant and other emerging NK1 receptor antagonists in patients receiving agents with a high risk of pruritus.[50]

Like aprepitant, orvepitant is an orally active, potent, brain-penetrant, and selective non-surmountable NK1 antagonist that blocks SP signalling.[51-53] These compounds are active in the well characterised NK1 receptor pharmacodynamic gerbil foot-tapping model, in preclinical models of anxiety,[51-54] and, as reported above, in the gerbil scratching behaviour model.[28,29] In humans both compounds have pharmacokinetic properties consistent with once-daily oral dosing sufficient to achieve therapeutic plasma exposures that have high levels of central NK1 receptor occupancy.[55,56] Thus, orvepitant would be expected to achieve antipruritic efficacy similar to that of aprepitant in patients suffering from intense itch as a result of EGFRI treatment. The RELIEVE 1 study evaluating

the efficacy and safety of orvepitant is the first randomised, double-blind, placebo-controlled study of an NK1 antagonist for EGFRI-induced pruritus.

METHODS

Patient and public involvement

The indication, research questions and study endpoint outcome measures were selected based on the authors expert understanding in the care of affected patients, their needs and therapy preferences, without direct communication of the study design to patients. Experience from guideline work, which involved patients preferences, was also carried over into the study design. Patients were not involved in the recruitment nor conduct of the study, nor the interpretation of results. No commitment was made to disseminate the results to study participants. Patients assessed the burden of the intervention themselves. Patients were not invited to contribute to the writing nor editing of this document for either readability or accuracy.

Study design and enrolment

The primary objective of this exploratory Phase 2, multicentre, randomised, double-blind, placebo-controlled clinical trial was to evaluate the efficacy of orvepitant compared with placebo in reducing the intensity of intense EGFRI-induced pruritus. Pruritus intensity was measured primarily by change from Baseline in patient-recorded numerical rating scale (NRS) score ranging from 0 (no itch) to 10 (worst itch imaginable) points. On the basis of an assumed between-patient standard deviation (SD) of 2 points,[8] 23 patients per treatment arm were required to provide 80% power for a 2-sided 5% significance level hypothesis test to achieve a significant result when the true difference is at least 2 points. It was thus planned to enrol 30 patients per arm (90 total). After 20 months of recruitment, this target was far from being reached, and a blinded analysis of data variance showing between-patient SD of 2.6 points indicated that it was highly unlikely that a statistically robust assessment of benefit could be made even if enrolment were completed. The sponsor decided to terminate enrolment. However, the study data for all enrolled patients were analysed.

Patients and treatments

Patients were enrolled at 15 hospitals in Italy and 5 hospitals in the United Kingdom between 13 November 2013 and 11 May 2015. Key eligibility criteria were age 18 years and older, monotherapy with an EGFRI (including cetuximab, panitumumab, erlotinib, gefitinib, lapatinib, and afatinib) for a histologically confirmed malignant solid tumour, moderate or intense pruritus after treatment with the EGFRI (defined as the mean of between 2 and 7 daily patient-reported average pruritus intensity NRS scores initially ≥7 and subsequently changed in April 2014 to ≥5 to improve study recruitment), pruritus treatment within the previous 3 months, and no use of aprepitant or fosaprepitant in the previous 4 weeks. The investigators randomised eligible patients according to a central randomisation code generated by the sponsor using an interactive voice response system (IVRS). The patients were assigned in a 1:1:1 ratio to receive 30 mg orvepitant, 10 mg orvepitant, or placebo tablets once daily (in the evening before bedtime) for 4 weeks. Randomisation was stratified by investigational site; block size was 6. Placebo tablets were identical in appearance to orvepitant tablets.

Assessments

Patients were followed-up for 4 weeks after treatment was completed or discontinued. Patients reported their NRS scores daily using an IVRS between Baseline and Week 8. At each study visit (Baseline, Week 1, Week 4, Week 8) an NRS score and a verbal rating scale (VRS) score were recorded. The VRS score was assigned in response to the following questions: How intense was your pruritus during the past 24 hours? Did you have no pruritus, weak pruritus, moderate pruritus, severe pruritus, or very severe pruritus? Scores ranged from 0 (no pruritus) to 4 (very severe pruritus). Both the NRS and VRS are validated instruments for the measurement of pruritus intensity.[57] At

each study visit, the patients also completed the Skindex-16 (an instrument to measure the effects of skin disease on health-related quality of life),[58] and the Leeds Sleep Evaluation Questionnaire (LSEQ; a 10-item instrument to assess changes in sleep quality over the course of an intervention). Safety was assessed by physical examination (including Eastern Cooperative Oncology Group [ECOG] status) and 12-lead electrocardiogram (ECG) at Baseline and Week 8, vital signs and laboratory tests (haematology, serum biochemistry, urinalysis) at each visit, and recording of AEs throughout the study. AEs were graded and categorised according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE). Use of concomitant medications, including EGFRIs and any rescue medication, was recorded throughout the study. Sparse pharmacokinetic sampling was conducted to allow for exploratory analysis of the correlation of orvepitant plasma levels with clinical efficacy and secondary assessment scores.

Endpoints

The primary endpoint was change from Baseline in mean patient-recorded NRS score (over the last 3 recordings) at Week 4. Secondary endpoints were also evaluated: change from Baseline in mean patient-recorded NRS score (last 3 recordings) each week; change from Baseline in mean patient-recorded NRS score (all values in the week) at Weeks 1, 4, 8; change from Baseline in patient-recorded NRS score at Days 2, 3, 4, 5, 6, 7, 8; change from Week 4 in patient-recorded NRS score (over the last 3 recordings) at Weeks 5, 6, 7, 8; change from Week 4 in VRS score at Week 8; change from Baseline in Skindex-16 quality of life at Weeks, 1, 4, 8; change from Baseline in LSEQ at Weeks, 1, 4, 8; rescue medication use; EGFRI dose reduction; and study withdrawal because of intense uncontrolled pruritus.

Statistical analysis

Efficacy endpoints were analysed in the modified intention-to-treat (mITT) population of all randomised patients who had received at least the first dose of study medication and had at least 1 post-treatment efficacy assessment. The primary endpoint was analysed by mixed-model repeated measures analysis with the primary inference being the change from Baseline in patient-reported NRS scores averaged across the last 3 values of the fourth week of dosing fitted as the response variable in the mixed model. The model included treatment group, study pooled site, study visit, the interaction between study visit and treatment group, the covariate (the baseline value of the variable being analysed) and the interaction between baseline covariate and visit. The 3 treatment groups were analysed together in one model. Point estimates and corresponding 95% confidence intervals were constructed for the difference between each dose of orvepitant and placebo for each week. The primary efficacy endpoint was tested at a 5% level of significance using a two-sided test to test orvepitant 30 mg versus placebo, and no adjustment for multiple comparisons was made for the patient-recorded NRS score orvepitant 10 mg versus placebo test or the secondary and exploratory endpoints. Safety was analysed in the safety population of all patients who received a dose of study medication using descriptive statistics.

RESULTS

Patients

A total of 44 patients were randomised and treated: 16 to orvepitant 30 mg, 14 to orvepitant 10 mg, and 14 to placebo. Nine patients discontinued the study (Figure 1). All patients were Caucasian, and 26 (59%) were male and 18 (41%) female. Median age was 68 years (range: 35 to 83 years), and 32 (73%) patients were aged 65 or older. Mean baseline NRS score ranged from 5.88 (SD: 0.93) in the placebo group to 6.68 (SD: 1.28) in the 30 mg orvepitant group. At Baseline, most patients had moderate to severe pruritus, and the most common locations were the head (specifically the scalp 26 [59%] patients) and the trunk (11 [25%]). Baseline assessments of acneiform rash and maculopapular rash showed a similar pattern (Table 1).

Table 1. Demographic and baseline characteristics

Characteristic	Orvepitant 30 mg *N* = 16	Orvepitant 10 mg *N* = 14	Placebo *N* = 14	Total *N* = 44
Age (years), median (range)	69.0 (43, 83)	73.5 (49, 81)	67.0 (35, 76)	68.0 (35, 83)
Age groups, n (%)				
< 65 years	4 (25.0)	4 (28.6)	4 (28.6)	12 (27.3)
≥ 65 years	12 (75.0)	10 (71.4)	10 (71.4)	32 (72.7)
Gender, n (%)				
Female	5 (31.3)	5 (35.7)	8 (57.1)	18 (40.9)
Male	11 (68.8)	9 (64.3)	6 (42.9)	26 (59.1)
Race, n (%)				
Caucasian	16 (100.0)	14 (100.0)	14 (100.0)	44 (100.0)
Time since cancer diagnosis (months), median (range)	17.5 (1, 131)	29.7 (12, 129)	20.8 (5, 60)	23.0 (1, 131)
Patient-reported NRS score				
Mean (SD)	6.68 (1.278)	6.95 (1.4.13)	5.88 (0.930)	NC
Median (range)	6.86 (4.8, 9.3)	7.00 (5.0, 10.0)	5.57 (5.0, 7.4)	NC
PRURITUS				
CTCAE grade, n (%)				
Grade 1	2 (12.5)	0	0	2 (4.5)
Grade 2	8 (50.0)	9 (64.3)	11 (78.6)	28 (63.6)
Grade 3	5 (31.3)	5 (35.7)	3 (21.4)	13 (29.5)
Unknown	1 (6.3)	0	0	1 (2.3)
Location, n (%)				
Head	8 (50.0)	6 (42.9)	12 (85.7)	26 (59.1)
Trunk	7 (43.8)	3 (21.4)	1 (7.1)	11 (25.0)
Arms	0	3 (21.4)	0	3 (6.8)
Legs	0	2 (14.3)	1 (7.1)	3 (6.8)
Unknown	1 (6.3)	0	0	1 (2.3)
ACNEIFORM RASH				
CTCAE grade, n (%)				
Grade 1	2 (12.5)	3 (21.4)	2 (14.3)	7 (15.9)
Grade 2	7 (43.8)	7 (50.0)	10 (71.4)	24 (54.5)
Grade 3	6 (37.5)	3 (21.4)	1 (7.1)	10 (22.7)
Unknown	1 (6.3)	1 (7.1)	1 (7.1)	3 (6.8)
Location, n (%)				
Head	7 (43.8)	5 (35.7)	11 (78.6)	23 (52.3)
Trunk	7 (43.8)	5 (35.7)	0	12 (27.3)
Arms	1 (6.3)	3 (21.4)	1 (7.1)	5 (11.4)
Legs	0	0	1 (7.1)	1 (2.3)
Unknown	1 (6.3)	1 (7.1)	1 (7.1)	3 (6.8)
MACULOPAPULAR RASH				

CTCAE grade, n (%)				
Grade 1	3 (18.8)	5 (35.7)	5 (35.7)	13 (29.5)
Grade 2	8 (50.0)	5 (35.7)	8 (57.1)	21 (47.7)
Grade 3	4 (25.0)	3 (21.4)	0	7 (15.9)
Unknown	1 (6.3)	1 (7.1)	1 (7.1)	3 (6.8)
Location, n (%)				
Head	7 (43.8)	5 (35.7)	12 (85.7)	24 (54.5)
Trunk	7 (43.8)	4 (28.6)	0	11 (25.0)
Arms	1 (6.3)	4 (28.6)	0	5 (11.4)
Legs	0	0	1 (7.1)	1 (2.3)
Unknown	1 (6.3)	1 (7.1)	1 (7.1)	3 (6.8)
CTCAE = Common Terminology Criteria for Adverse Events; NC = not calculated; NRS = numerical rating scale; SD = standard deviation.				

The median dose number was 28 (range: 1 to 35) in the 30 mg group, 28 (range: 1 to 35) in the 10 mg group, and 29 (range: 28 to 39) in the placebo group. Five (11%) patients (all in the orvepitant groups) took the study drug for 1 week or less; 18 (41%) patients took the study drug (orvepitant or placebo) for 1 to 4 weeks, and 21 (48%) took the study drug for >4 weeks (maximum: 39 days).

All 44 patients were included in the mITT and safety populations and analysed according to the randomised treatment.

Efficacy

Patient compliance with daily reporting of NRS score was high; mean compliance rate was 92%, and median compliance rate was 100%. At Week 4, 38 subjects remained in the study. NRS score decreased from Baseline to Week 4 in all 3 groups (Table 2). The difference between orvepitant and placebo was not, however, statistically significant (30 mg group: $P = 0.12$, 10 mg group: $P = 0.19$).

Table 2. Change from Baseline in patient-reported numerical reporting scale scores at Week 4

Statistic	Orvepitant 30 mg *N* = 16	Orvepitant 10 mg *N* = 14	Placebo *N* = 14
n	**13**	**11**	**14**
Mean (SD)	-2.78 (2.64)	-3.04 (3.06)	-3.21 (1.77)
Median	-2.75	-2.00	-2.50
Minimum, maximum	-6.3, 3.0	-8.3, 1.1	-6.3, 0.0
LSMEANS estimate (95% CI)	-2.40 (-3.54, -1.27)	-2.53 (-3.80, -1.27)	-3.70 (-4.88, -2.52)
LSMEANS standard error	0.56	0.62	0.58
Orvepitant vs placebo difference (95% CI)	1.30 (-0.35, 2.95)	1.17 (-0.62, 2.96)	
P value	0.120	0.194	
CI = confidence interval; LSMEANS = least-squares means; SD = standard deviation.			

Note: Analysis results from mixed-model repeated measures analysis (Week 1 to Week 4) of the 3 treatment groups analysed together in one model: Change from Baseline = Treatment + Pooled Site + Visit + Treatment*Visit + Baseline Results + Visit*Baseline Covariate Interaction

Secondary NRS and VRS endpoints reflected the results for the primary endpoint (Table 3). Change from Baseline in Skindex-16 and LSEQ score showed no difference between the treatment groups at any time point. Rescue medication use and EGFRI dose reduction both occurred in 7 (16%) patients (3 in the orvepitant 30 mg group and 2 each in the orvepitant 10 mg and placebo groups). No subjects withdrew from the study because of intense uncontrolled pruritus.

Table 3. Summary of secondary efficacy endpoints

Statistic	Orvepitant 30 mg *N* = 16	Orvepitant 10 mg *N* = 14	Placebo *N* = 14
Change from Baseline, (n) Mean (SD)			
Patient-recorded NRS score (last 3 recordings) at Week 1	(16) -1.18 (1.55)	(13) -1.66 (2.48)	(14) -1.16 (1.41)
Patient-recorded NRS score (last 3 recordings) at Week 2	(14) -2.33 (2.00)	(13) -2.85 (3.43)	(13) -2.76 (1.96)
Patient-recorded NRS score (last 3 recordings) at Week 3	(14) -2.16 (2.56)	(11) -3.14 (2.77)	(14) -3.26 (2.00)
Patient-recorded NRS score (last 3 recordings) at Week 5	(13) -3.19 (2.88)	(10) -3.32 (3.19)	(14) -3.90 (2.19)
Patient-recorded NRS score (last 3 recordings) at Week 6	(13) -3.24 (2.89)	(10) -3.68 (2.55)	(13) -4.00 (1.78)
Patient-recorded NRS score (last 3 recordings) at Week 7	(12) -2.49 (2.91)	(10) -2.85 (2.52)	(12) -4.13 (2.33)
Patient-recorded NRS score (last 3 recordings) at Week 8	(11) -2.86 (2.91)	(10) -3.18 (2.68)	(12) -4.32 (2.27)
Patient-recorded NRS score (all week) at Week 1	(16) -0.96 (1.09)	(13) -1.34 (1.93)	(14) -0.86 (1.00)
Patient-recorded NRS score (all week) at Week 4	(13) -2.64 (2.61)	(11) -3.05 (3.00)	(14) -3.20 (1.96)
Patient-recorded NRS score (all week) at Week 8	(11) -2.65 (2.81)	(10) -3.15 (2.66)	(12) -4.29 (2.33)
Clinic-visit NRS score at Week 1	(14) -1.93 (1.73)	(14) -2.21 (3.19)	(14) -3.00 (2.60)
Clinic-visit NRS score at Week 4	(13) -3.38 (2.69)	(11) -4.27 (2.94)	(14) -4.14 (2.18)
Clinic-visit NRS score at Week 8	(13) -3.50 (2.71)	(11) -3.91 (2.66)	(12) -3.92 (2.35)
Patient-recorded NRS score at Day 2	(16) -0.61 (1.29)	(12) -0.84 (1.24)	(13) -0.33 (0.74)
Patient-recorded NRS score at Day 3	(14) -0.96 (0.99)	(11) -0.86 (1.64)	(13) -0.41 (0.65)
Patient-recorded NRS score at Day 4	(14) -0.85 (1.09)	(12) -1.04 (1.88)	(14) -0.81 (1.28)
Patient-recorded NRS score at Day 5	(13) -1.35 (1.12)	(12) -1.29 (2.23)	(13) -1.18 (1.45)
Patient-recorded NRS score at Day 6	(14) -1.28 (1.68)	(11) -1.31 (2.20)	(11) -1.30 (1.54)
Patient-recorded NRS score at Day 7	(14) -1.42 (2.30)	(12) -1.87 (3.63)	(13) -1.33 (1.89)
Patient-recorded NRS score at Day 8	(14) -1.85 (2.31)	(11) -1.83 (2.42)	(14) -1.88 (2.03)
Skindex-16 at Week 1: Symptoms	(14) -12.56 (22.25)	(13) 1.24 (25.05)	(13) -2.88 (18.50)

Skindex-16 at Week 4: Symptoms	(13) -8.29 (25.06)	(11) -9.09 (36.94)	(13) -7.69 (29.56)
Skindex-16 at Week 8: Symptoms	(12) -8.09 (23.60)	(11) -8.71 (36.19)	(12) -4.02 (33.30)
Skindex-16 at Week 1: Emotions	(14) -44.73 (16.35)	(13) -21.52 (27.80)	(13) -21.29 (18.20)
Skindex-16 at Week 4: Emotions	(13) -32.60 (24.96)	(11) -31.96 (36.34)	(13) -25.69 (26.54)
Skindex-16 at Week 8: Emotions	(12) -35.37 (30.88)	(11) -37.23 (28.13)	(12) -36.86 (26.32)
Skindex-16 at Week 1: Functioning	(14) -13.33 (16.69)	(13) -12.05 (29.08)	(13) -1.28 (13.51)
Skindex-16 at Week 4: Functioning	(13) 2.05 (26.51)	(11) -11.51 (36.07)	(13) -1.80 (20.40)
Skindex-16 at Week 8: Functioning	(12) -0.83 (28.04)	(11) -22.73 (25.64)	(12) -5.00 (16.17)
LSEQ at Week 1: Getting to sleep	(13) -12.08 (22.10)	(12) -9.82 (23.50)	(12) -6.45 (16.97)
LSEQ at Week 4: Getting to sleep	(12) -12.36 (19.61)	(9) 3.37 (23.64)	(12) -8.47 (18.19)
LSEQ at Week 8: Getting to sleep	(11) -4.57 (13.67)	(9) 2.04 (25.47)	(11) -7.06 (23.68)
LSEQ at Week 1: Quality of sleep	(13) -6.77 (26.98)	(12) -13.29 (33.39)	(12) -5.67 (15.39)
LSEQ at Week 4: Quality of sleep	(12) -6.46 (20.63)	(9) -8.61 (39.09)	(12) -9.13 (17.60)
LSEQ at Week 8: Quality of sleep	(11) -6.73 (21.81)	(9) -17.22 (34.00)	(11) -10.14 (26.73)
LSEQ at Week 1: Awake following sleep	(13) 5.85 (19.80)	(12) -12.08 (32.39)	(12) -2.04 (15.50)
LSEQ at Week 4: Awake following sleep	(12) 8.29 (16.22)	(8) -8.00 (43.83)	(12) -4.13 (19.93)
LSEQ at Week 8: Awake following sleep	(11) 7.23 (16.91)	(9) -10.72 (36.14)	(11) -7.55 (30.06)
LSEQ at Week 1: Behaviour following wakening	(13) 3.90 (12.44)	(12) -3.89 (32.06)	(12) -3.67 (7.67)
LSEQ at Week 4: Behaviour following wakening	(12) 1.03 (15.97)	(9) 5.78 (46.41)	(12) -9.89 (14.53)
LSEQ at Week 8: Behaviour following wakening	(11) -0.36 (13.73)	(9) 6.82 (49.17)	(11) -1.82 (19.95)
Change from Baseline, n (%)			
VRS score at Week 1			
Improved	8 (57.1)	9 (64.3)	9 (64.3)
No change	5 (35.7)	3 (21.4)	4 (28.6)
Worsened	1 (7.1)	2 (14.3)	1 (7.1)
VRS score at Week 4			
Improved	10 (76.9)	8 (80.0)	11 (78.6)
No change	3 (23.1)	2 (20.0)	2 (14.3)
Worsened	0	0	1 (7.1)
VRS score at Week 8			
Improved	9 (75.0)	9 (81.8)	9 (81.8)
No change	3 (25.0)	2 (18.2)	2 (18.2)
Worsened	0	0	0
Change from Week 4, (n) Mean (SD)			
Patient-recorded NRS score (last 3 recordings) at Week 5	(13) -0.41 (1.409)	(10) -0.47 (1.989)	(14) -0.69 (0.991)
Patient-recorded NRS score (last 3 recordings) at Week 6	(13) -0.46 (1.561)	(10) -0.83 (2.196)	(13) -0.69 (0.897)
Patient-recorded NRS score (last 3 recordings) at Week 7	(12) 0.17 (1.972)	(10) 0.00 (3.604)	(12) -0.72 (1.127)
Patient-recorded NRS score (last 3 recordings) at Week 8	(11) -0.42 (2.071)	(10) -0.33 (3.728)	(12) -0.92 (1.084)
VRS score at Week 8	(12) -0.08 (1.730)	(11) 0.36 (3.501)	(12) 0.08 (1.165)
Number of Subjects (%)			
Prescribed rescue medication	6 (37.5)	4 (28.6)	2 (14.3)
Used rescue medication	3 (18.8)	2 (14.3)	2 (14.3)

EGFRI dose reduction	3 (18.8)	2 (14.3)	2 (14.3)
Withdrawal because of intense uncontrolled pruritus	0	0	0
EGFRI = epidermal growth factor receptor inhibitor: LSEQ = Leeds Sleep Evaluation Questionnaire; NRS = numerical rating scale; SD = standard deviation; VRS = verbal rating scale.			

Analyses of pharmacokinetic data were not conducted because of the lack of efficacy observed.

Safety

No safety signal was detected. A total of 34 (77%) patients experienced a treatment-emergent AE, but no unexpected AEs were reported. Only 4 mild and moderate AEs were considered by investigators to be related to orvepitant (Table 4). AEs that occurred in >5% of patients were asthenia (8 [18%] patients), skin toxicity (7 [16%] patients; term reported by the investigators was skin toxicity, which for EGFRIs commonly includes reactions such as skin rash, skin dryness [xerosis], pruritus, paronychia, hair abnormality, mucositis, and increased, growth of the eyelashes or facial hair[59]), diarrhoea (4 [9%] patients), cough (3 [7%] patients), rash (3 [7%] patients; terms as reported by the investigators included worsening of rash; hands, ankle and face rash; and rash cutaneous), and anaemia (3 [7%] patients). These more common AEs occurred in similar rates in the active and placebo groups except for anaemia and rash, which occurred infrequently and only in patients who received orvepitant. There was no apparent relationship between incidence or severity of AEs and orvepitant dose. No serious AEs were reported.

Table 4. Drug-related adverse events

	Orvepitant 30 mg *N* = 16 n (%)	**Orvepitant 10 mg *N* = 14 n (%)**	**Placebo *N* = 14 n (%)**
Any drug-related AE	3 (18.8)	1 (7.1)	0
Mild AEs			
Asthenia	1 (6.3)	0	0
Dizziness	0	1 (7.1)	0
Dry mouth	1 (6.3)	0	0
Moderate AEs			
Hyperhidrosis	1 (6.3)	0	0

No clinically significant changes in laboratory results, vital signs, physical examination findings, ECOG status, or ECG parameters were related to orvepitant.

DISCUSSION

Interpretation of the results

Orvepitant appeared safe and well tolerated, and the findings in this study are consistent with the substantial safety database accumulated to date on this product in different populations. The safety profile exhibited allows further investigation of orvepitant in this or other indications, including a planned Phase 3 study in refractory or unexplained chronic cough following a successful Phase 2 study in this indication.[60]

The efficacy results were, however, inconclusive; no significant difference between the active groups and the placebo group was observed. Patients experienced a mean reduction in itching of approximately 3 NRS points in the 2 orvepitant groups and the placebo group. This outcome may, of course, have resulted from the premature

termination of the study and the consequent substantially reduced sample size making it difficult to determine a treatment difference. However, given there was no indication of difference between the arms, it seems unlikely even if the study had been fully recruited that a treatment effect would have been detected. This outcome stands in stark contrast to the observation studies conducted with the NK1 antagonist aprepitant.[33-49] For example, in a 1-week, open-label study in 45 patients experiencing mainly EGFRI-induced severe pruritus, aprepitant therapy resulted in median visual analogue scale itch scores falling from 8 at Baseline to 1 after 7 days in a refractory group resistant to standard anti-pruritus treatments and from 8 to 0 in a naive group ($p<0.0001$ in both groups).[8] In this trial 41 (91%) patients responded to aprepitant (i.e., had a >50% reduction in pruritus intensity), and pruritus recurred in only 6 (13%) patients. This difference is difficult to rationalise given that the pharmacology of orvepitant and aprepitant are so comparable and both can achieve exposures likely to be therapeutic in humans following oral dosing. However, one plausible explanation for the results in the RELIEVE 1 study is the placebo effect that is often seen in clinical trials with subjective endpoints such as pruritus intensity.[61] In this study, critically ill patients were receiving a modern antineoplastic therapy, and they may have had a particularly high expectation of the benefit of their EGFRI therapy in general and of orvepitant's ability to reduce pruritus and thereby improve their quality of life.

A further explanation for the RELIEVE 1 study results relates to the pathological mechanism underlying the itch in these patients. EGFRI-induced pruritus arises acutely within the first 2 weeks after initiation of the anticancer therapy[5] and cutaneous accumulation, and activation of dermal mast cells[16,17,62] may be the most important driver of the itch signalling in these patients. This acute course contrasts with that of chronic pruritus conditions (defined as being >6 weeks in duration),[63] which are now linked to the sensitisation of itch signalling pathways similar to chronic pain, such that patients may report spontaneous itch (alloknesis) or an enhanced itch to normal itch-evoking stimuli (hyperknesis).[32,64,65] NK1 antagonists have shown great promise in randomised, placebo-controlled clinical studies as treatments for chronic pruritus conditions in general[66,67] as well as specifically for prurigo nodularis,[68] atopic dermatitis-associated pruritus,[69] and psoriasis-associated pruritus.[70] Orvepitant has shown efficacy against chronic refractory cough, which has also been recognised as a neural hypersensitivity syndrome.[60] Thus, NK1 antagonists may lack efficacy in acute pruritic conditions driven by cutaneous mast cells, such as EGFRI-induced pruritus, whilst being effective in chronic pruritus conditions by addressing itch pathway sensitisation.

A final explanation is that the improvement in itch scores seen in the 2 orvepitant groups and the placebo group may be attributable to the natural course of pruritus over the weeks following the initiation of EGFRI treatment. It is now known that patterns of cutaneous toxicities with EGFRI treatment can vary with time; for example, the intensity of acneiform rash that is associated with pruritus rises and falls dramatically in the first month.[71] If this were the case for itch intensity, it would be difficult to show a benefit against such a dynamic and self-limiting background.

Strengths and limitations of the study

The RELIEVE 1 study was the first randomised, double-blind, placebo-controlled study of an NK1 receptor antagonist for EGFRI-induced pruritus. The enrolment target was not reached because of recruitment problems in the critically ill target population. A similar response was seen in both placebo and active groups, a result for which there are several possible explanations. Nonetheless, this randomised, controlled study provided insights into the course, itch characteristics, and possible mechanisms of EGFRI-induced pruritus that may inform future studies.

Implications for future studies

Recruitment for this study was stopped after 20 months when only 44 of the planned 90 subjects had been enrolled. Despite evidence in the literature of a high prevalence of EGFRI-induced pruritus,[1-11,13,50,72,73] we experienced substantial difficulty identifying patients with severe enough pruritus (i.e., NRS score ≥ 5) to enable detection of post-treatment change. Study enrolment may have been limited by the fact that all investigators were oncologists, who are faced with multiple AEs in patients receiving EGFRIs (e.g., diarrhoea, rash, asthenia, nausea and vomiting, conjunctivitis, mucositis) that may have taken precedence over pruritus, a purely subjective symptom that is not

widely reported in the oncology community.[10] Patients may also have been unwilling to enter the study because pruritus is not a major priority for them compared to their cancer.

NK1 antagonists may still hold potential for treatment of skin toxicities experienced by cancer patients treated with EGFRIs or other targeted therapies. However, future studies will require a more complete understanding of the epidemiology and course of target cancer therapy-induced pruritus to enable appropriate selection and sizing of the patient population to achieve statistical power and a design that minimises or quantifies the placebo effect. Furthermore, greater knowledge of the pathological mechanism underlying the pruritus in this condition is needed. Without these advances, the experience of this trial shows that further investigation of this particular drug-induced pruritus condition at the current juncture will prove challenging.

FIGURE LEGENDS

Figure 1. Disposition of RELIEVE 1 patients

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Competing interests MT is a current employee and ER is a past employee of NeRRe Therapeutics Ltd, and both are inventors on a granted patent on novel uses of orvepitant. BV and PG received payment from NeRRe as investigators in this study. AD received payment from NeRRe for service as the Chief Medical Officer for this study. DJ is an employee of Cromsource, which received payment from NeRRe for statistical analysis of this study. PH has received payment from NeRRe as a consultant. ML reports receiving personal fees from Legacy Healthcare Services, AdgeroBio Pharmaceuticals, Amryt Pharma, Celldex Therapeutics, Debiopharm, Galderma Research and Development, Johnson & Johnson, Novocure, Lindi Skin, Merck Sharp and Dohme Corporation, Helsinn Healthcare SA, Janssen Research & Development LLC, Menlo Therapeutics, Novartis Pharmaceuticals Corporation, F. Hoffmann-La Roche AG, Abbvie Inc. Boehringer Ingelheim Pharma Gmbh & Co. KG, Allergan Inc, Amgen Inc, E.R. Squibb & Sons L.L.C., EMD Serono Inc, AstraZeneca Pharmaceuticals LP, Genentech Inc, Leo Pharma Inc, Seattle Genetics, Bayer, Männer SAS, Lutris Pharma, Pierre Fabre, Paxman Cooler Ltd, Adjucare, Dignitana, Biotechspert, Teva Pharmaceuticals Mexico, Parexel, OnQuality Pharmaceuticals Ltd, Novartis, Our Brain Bank, Millenium Pharmaceuticals and research funding from Berg Health, Bristol-Myers Squibb, Lutris Pharma, Novocure, Paxman, Biotest, and Veloce BioPharma. GT reports no conflicts of interest. AW reports receiving payment from NeRRe as Chair of the Advisory Board and from Advent Life Sciences for consultancy, Canbex Therapeutics as a nonexecutive director (past position), Calcico Therapeutics as chairman (past position) and a nonexecutive director (past position), and the Wellcome Trust as a member of grant committees. SS reports receiving payment from NeRRe as a member of the advisory board and from Almirall, Astellas Pharma, Beiersdorf, Celgene Corporation, Chugai Pharma, Creabilis, Daiichi Sankyo, Galderma, Helsinn, Kiniska Pharmaceuticals, Kneipp, Maruho Co, Merz Pharma, Novartis, Pierre Fabre Laboratories, Sienna Biopharmaceuticals, and Ziarco as a member of their advisory boards and from Menlo Therapeutics as an investigator and participation as an investigator in trials sponsored by Dermascence, Trevi Therapeutics, and Vanda Pharmaceuticals.

Patient consent All patients provided written informed consent for participation before enrolment in the trial.

Ethics approval This trial was approved by NRES Committee North East - Tyne & Wear South for the UK investigational sites and Comitato etico dell'Università Campus Bio-Medico di Roma for those in Italy.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The deidentified data set for this study is available upon reasonable request from the study sponsor NeRRe Therapeutics Ltd.

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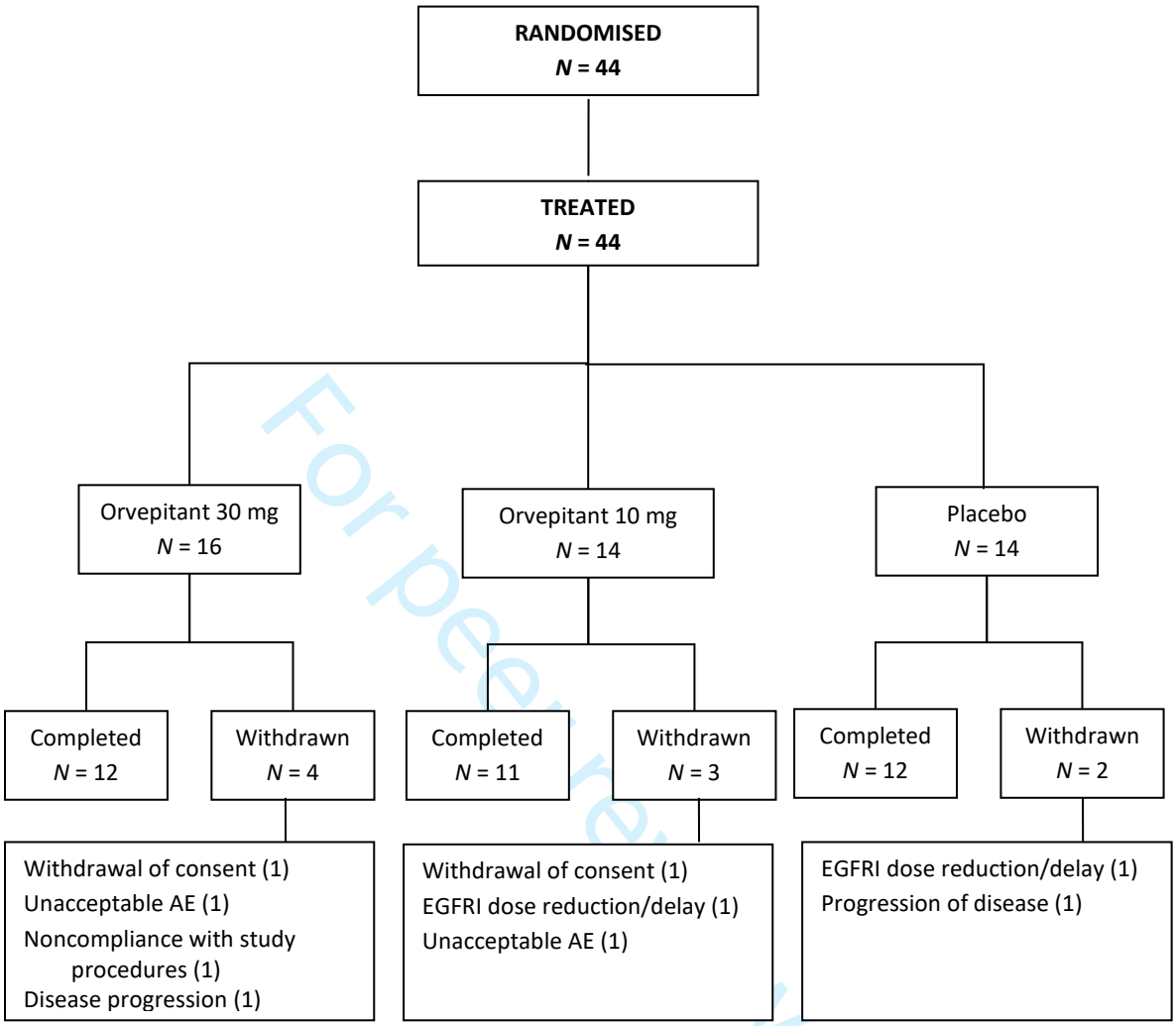

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3, 4
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	4
Participants	4a	Eligibility criteria for participants	4
	4b	Settings and locations where the data were collected	4
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	4
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	4, 5
	6b	Any changes to trial outcomes after the trial commenced, with reasons	Not applicable
Sample size	7a	How sample size was determined	4
	7b	When applicable, explanation of any interim analyses and stopping guidelines	Not applicable
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	4
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	4
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	4
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	4

Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	4
	11b	If relevant, description of the similarity of interventions	4
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	5
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	Not applicable
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	5, 6
	13b	For each group, losses and exclusions after randomisation, together with reasons	Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	4
	14b	Why the trial ended or was stopped	8,9
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	5, 6
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	7
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	7, 8 and 9
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Not applicable
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Not applicable
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	8
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	8
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	8, 9
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	8, 9
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	Not applicable
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	10

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.