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

Bruno Vincenzi ![ORCID],[1] Mike Trower ![ORCID],[2] Ajay Duggal ![ORCID],[3] Pamela Guglielmini ![ORCID],[4] Peter Harris ![ORCID],[2] David Jackson ![ORCID],[5] Mario E Lacouture ![ORCID],[6] Emiliangelo Ratti ![ORCID],[2] Giuseppe Tonini ![ORCID],[1] Andrew Wood ![ORCID],[7] Sonja Ständer ![ORCID] [8]

For numbered affiliations see end of article.

Correspondence to
Dr Mike Trower;
mike.trower@nerretherapeutics.com

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 five hospitals in the UK.

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 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 three 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 EudraCT2013-002763-25.

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 epidermal growth factor receptor inhibitor-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 (AE), particularly dermatological AEs, including acneiform rash, hair changes, mucositis, xerosis/fissures, paronychia and pruritus. Epidermal growth factor receptor inhibitors (EGFRI) 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 (mAb) and small-molecule EGFRIs ranges from 8% to 69% depending on the agent involved.[8 9] EGFRI-induced pruritus may be under-reported or incompletely reported in clinical studies.[10] In a survey of patients with cancer and survivors, pruritus is common and debilitating.[11 12] Lacouture *et al* reported that pruritus occurs in approximately half of all patients treated

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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, 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 have 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 an 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 II, multi-centre, 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 SD of 2 points,[8] 23 patients per treatment arm were required to provide 80% power for a two-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 the enrolment. However, the study data for all enrolled patients were analysed.

Patients and treatments

Patients were enrolled at 15 hospitals in Italy and five hospitals in the UK 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 the 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 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. 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 three recordings) at week 4. Secondary endpoints were also evaluated: change from baseline in mean patient-recorded NRS score (last three 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 three 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 one 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 three treatment groups were analysed together in one model. Point estimates and corresponding 95% CIs 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: 35–83 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).

The median dose number was 28 (range: 1–35) in the 30 mg group, 28 (range: 1–35) in the 10 mg group and 29 (range: 28–39) in the placebo group. Five (11%) patients (all in the orvepitant groups) took the study drug for 1 week
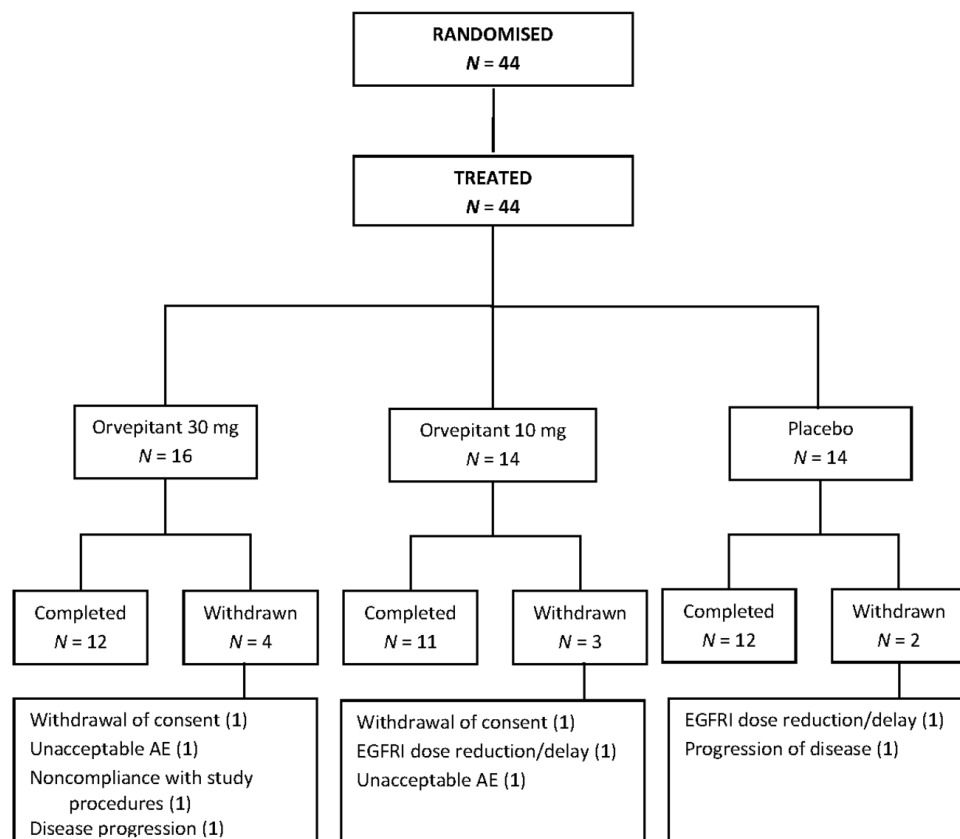
Figure 1 Disposition of RELIEVE 1 patients. AE, adverse event; EGFRI, epidermal growth factor receptor inhibitor.

or less; 18 (41%) patients took the study drug (orvepitant or placebo) for 1–4 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 patients remained in the study. NRS score decreased from baseline to week 4 in all three 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).

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 (three in the orvepitant 30 mg group and two each in the orvepitant 10 mg and placebo groups). No patients 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 four 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.

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,

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 (1.413)	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)

Continued

Table 1 Continued

Characteristic	Orvepitant 30 mg n=16	Orvepitant 10 mg n=14	Placebo n=14	Total n=44
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.

including a planned phase III study in refractory or unexplained chronic cough following a successful phase II 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 two 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 antipruritus 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 (ie, had a >50% reduction in pruritus intensity), and pruritus recurred in only 6 (13%) patients. This difference is difficult to rationalise given that the pharmacologies 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, patients who are critically ill 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]

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 to 3.0	−8.3 to 1.1	−6.3 to 0.0
LSMEANS estimate (95% CI)	−2.40 (−3.54 to −1.27)	−2.53 (−3.80 to −1.27)	−3.70 (−4.88 to −2.52)
LSMEANS SE	0.56	0.62	0.58
Orvepitant versus placebo difference (95% CI)	1.30 (−0.35 to 2.95)	1.17 (−0.62 to 2.96)	
P value	0.120	0.194	

Analysis results from mixed-model repeated measures analysis (week 1 to week 4) of the three treatment groups analysed together in one model: change from baseline=treatment+pooled site+visit+treatment*visit+baseline results+visit*baseline covariate interaction.
LSMEANS, least-squares means.

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 three recordings) at week 1	(16) −1.18 (1.55)	(13) −1.66 (2.48)	(14) −1.16 (1.41)
Patient-recorded NRS score (last three recordings) at week 2	(14) −2.33 (2.00)	(13) −2.85 (3.43)	(13) −2.76 (1.96)
Patient-recorded NRS score (last three recordings) at week 3	(14) −2.16 (2.56)	(11) −3.14 (2.77)	(14) −3.26 (2.00)
Patient-recorded NRS score (last three recordings) at week 5	(13) −3.19 (2.88)	(10) −3.32 (3.19)	(14) −3.90 (2.19)
Patient-recorded NRS score (last three recordings) at week 6	(13) −3.24 (2.89)	(10) −3.68 (2.55)	(13) −4.00 (1.78)
Patient-recorded NRS score (last three recordings) at week 7	(12) −2.49 (2.91)	(10) −2.85 (2.52)	(12) −4.13 (2.33)
Patient-recorded NRS score (last three 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			

Continued

Table 3 Continued

Statistic	Orvepitant 30 mg n=16	Orvepitant 10 mg n=14	Placebo n=14
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 three recordings) at week 5	(13) −0.41 (1.409)	(10) −0.47 (1.989)	(14) −0.69 (0.991)
Patient-recorded NRS score (last three recordings) at week 6	(13) −0.46 (1.561)	(10) −0.83 (2.196)	(13) −0.69 (0.897)
Patient-recorded NRS score (last three recordings) at week 7	(12) 0.17 (1.972)	(10) 0.00 (3.604)	(12) −0.72 (1.127)
Patient-recorded NRS score (last three 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)
Patients, n (%)			
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; VRS, verbal rating scale.

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, while being effective in chronic pruritus conditions by addressing itch pathway sensitisation.

A final explanation is that the improvement in itch scores seen in the two 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

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

AE, adverse event.

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 patients 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 (ie, 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 (eg, 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 with their cancer.

NK1 antagonists may still hold potential for treatment of skin toxicities experienced by patients with cancer 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.

Author affiliations
[1]Medical Oncology, Universita Campus Bio-Medico di Roma Facolta di Medicina e Chirurgia, Roma, Italy
[2]NeRRe Therapeutics, Stevenage, UK
[3]Adnovate Clinical Development Strategies, East Sussex, UK
[4]Oncology Unit, ASO SS Antonio e Biagio e C Arrigo, Alessandria, Italy
[5]Biometrics Division, Cromsource, Stirling, UK
[6]Department of Dermatology, Memorial Sloan Kettering Cancer Center, New York, New York, USA
[7]Idfac, Devon, UK
[8]Center for Chronic Pruritus, University Hospital Münster, Münster, Germany

ORCID iDs
Bruno Vincenzi http://orcid.org/0000-0001-8222-9025
Mike Trower http://orcid.org/0000-0003-0412-5719
Ajay Duggal http://orcid.org/0000-0003-3294-616X
Pamela Guglielmini http://orcid.org/0000-0003-3612-7786
Peter Harris http://orcid.org/0000-0002-8374-3859
David Jackson http://orcid.org/0000-0002-4448-8648
Mario E Lacouture http://orcid.org/0000-0002-4818-3710
Emiliangelo Ratti http://orcid.org/0000-0002-7352-4695
Giuseppe Tonini http://orcid.org/0000-0003-4442-8677
Andrew Wood http://orcid.org/0000-0001-7536-6398
Sonja Ständer http://orcid.org/0000-0003-3612-7786

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