The neurokinin-1 receptor antagonist orvepitant improves chronic cough symptoms: results from a Phase 2b trial

J. Smith[1], E. Ballantyne[2], M. Kerr[2], L. McGarvey[3], A. Morice[4], M. Sher[5], M. Trower[2], S. Pawsey[2]

[1]University of Manchester - Manchester (UK), [2]NeRRe Therapeutics Ltd - Stevenage (UK), [3]Queen's University Belfast - Belfast (UK), [4]Hull York Medical School - Cottingham (UK), [5]Center for Cough - Largo, Florida (USA)

Introduction

- Refractory or unexplained chronic cough (RUCC) is common and debilitating and has a major impact on patients' quality-of-life.[1] There are no proven therapies for RUCC, and treatments used off label include first generation antihistamines, antidepressants and opioids, with mixed results.
- RUCC is recognised as being a neural hypersensitivity disorder which results in cough being triggered by innocuous or/and low-level stimuli.[2] There is a strong rationale based on preclinical and human data that centrally acting NK_1 antagonists can modulate this neural dysfunction and be effective treatments for the excessive coughing experienced by RUCC patients.
- Orvepitant is a potent and selective antagonist of the NK_1 receptor. Initial evidence of efficacy as a treatment for RUCC was established in a Phase 2 open-label pilot study (VOLCANO-1).[3] The NK1 antagonist aprepitant has also shown efficacy in chronic cough due to lung cancer.[4]
- This study (VOLCANO-2, Clinicaltrials.gov identifier NCT02993822) was undertaken to further evaluate the efficacy and safety of orvepitant in RUCC and to establish the dose to take forward into future studies

Methods

Design

- The study was randomised, double-blind and placebo controlled. Subjects were recruited from 55 sites in the UK, USA and Canada
- Subjects were randomised to placebo or one of three doses of orvepitant (10 mg, 20 mg or 30 mg) once daily for 12 weeks
- Cough frequency (CF) was measured for 24-hour periods at baseline and at weeks 2, 4 and 12 using a VitaloJAK™ cough monitor (Vitalograph, Buckingham UK)
- Patient reported outcomes (PROs) were measured at Weeks 2, 4, 8 & 12. These were Leicester Cough Questionnaire (LCQ), cough severity and urge to cough visual analogue scales (VAS), and global ratings of change (GRC) in cough frequency and cough severity.

Analysis

- Change in awake CF was designated as the primary efficacy endpoint. Cough data were log-transformed for analysis
- Pre-specified analysis sub-groups of lower (< study median) or higher (≥ study median) cough frequency at baseline were defined although the study was only powered for analysis of the FAS

Subjects

- Subjects had ≥1-year history of cough which was not due to an identifiable underlying cause and/or not responsive to treatment
- Subjects had to have a baseline awake cough frequency ≥10 coughs/hour to be eligible
- 315 subjects were randomised of whom 275 were evaluable for efficacy (full analysis set [FAS]). All subjects were evaluated for safety.

Table 1: Baseline Cough Burden Characteristics for Each Analysis Group

Analysis Group	Lower Frequency Cough Group	Full Analysis Set	Higher Frequency Cough Group
N	150	315	156
Cough duration (mean, years)	12.8	12.8	12.8
Awake cough frequency (mean, coughs/hour)	20.2	43.0	66.7
Cough severity VAS – Day (mean, mm)	63.6	67.6	71.8
Cough severity VAS – Night (mean, mm)	42.1	43.5	45.5
Urge to cough VAS (mean, mm)	67.2	70.4	73.8
LCQ (Mean total score)	11.05	10.6	10.1

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Bibliography

1. Birring SS et al. Thorax 2003;58:339-343.
2. Chung KF. Pulm Pharmacol Ther. 2011 Jun;24(3):267-71.
3. Smith J, et al. CHEST 2019. doi: https://doi.org/10.1016/j.chest.2019.08.001.
4. Harle A, Smith J et al. J. Clin. Oncol. 2015 33:29_suppl, 2-2.
5. Abdulqawi R et al, *Lancet* 2015; **385:** 1198–205.

Results

Demographics & Disease Characteristics

- Subjects were predominantly female (80.3%), had a mean age of 61.0 years, and were mostly white (94.6%)
- Mean cough frequency at baseline was markedly different in the FAS, and lower and higher CF groups; however all other measures of disease burden were similar (Table 1)

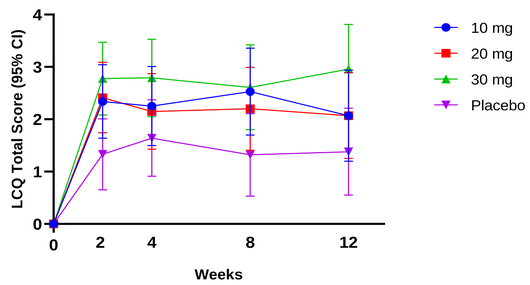
Patient Reported Outcomes

- All PROs were improved with orvepitant (all doses) compared to placebo at all time points in the full analysis set. The improvements were most evident for the 30 mg dose group (Table 2, Figure 1). Global ratings of change (data not shown) also supported these findings.
- The improvements compared to placebo (treatment difference) in the PROs were greater in the higher frequency group (Table 2)

Table 2: Patient reported outcomes at week 12 for orvepitant 30 mg

Orvepitant 30 mg versus Placebo at Week 12	Full Analysis Set		Higher Frequency Cough Group	
	Treatment Difference	p-value	Treatment Difference	p value
LCQ Total Score	1.6	0.009	1.9	0.041
Cough severity VAS (mean in mm)	-9.0	0.046	-14.6	0.018
Urge to cough VAS (mean in mm)	-11.8	0.005	-16.1	0.007

Figure 1: Change from baseline in LCQ total score (FAS)



Awake Cough Frequency

- The CF endpoint was not significant in the FAS due to an exaggerated placebo response at Week 12, most evident in the lower CF subjects (Figure 2)
- In the higher CF subjects (≥study median awake CF at baseline), a greater efficacy signal is evident with 30mg orvepitant; geometric mean ratio vs placebo 0.71 (95% CI 0.49, 1.02, p=0.066, Figure 3) with a greater proportion of subjects responding by at least 30% (70.0% vs 43.8%, p=0.009, Figure 4)

Figure 2: Awake Cough Frequency in the Full Analysis Set

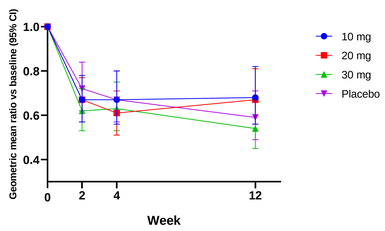


Figure 3: Awake Cough Frequency in the Higher Frequency Cough Group

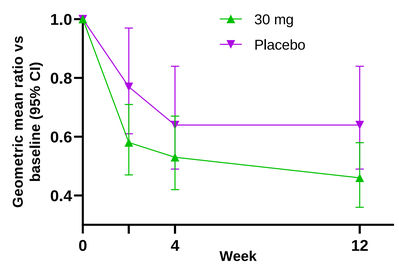
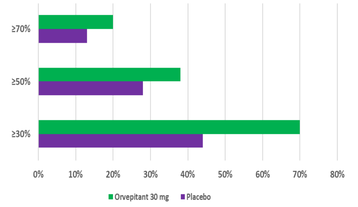


Figure 4: Awake Cough Frequency Responder Analysis in Higher Frequency Cough Group



Safety

- The proportion of patients with adverse events (AEs) was similar in all treatment groups (placebo 68.4%, orvepitant 66.7% to 72.2%). A few more orvepitant 30 mg subjects had treatment related AEs (13.9% vs 11.4%) but the number of subjects withdrawing due to related AEs was very low; placebo 0, orvepitant 30 mg 2 (2.5%).
- Adverse events more common with orvepitant 30 mg than placebo were headache (8.9% vs 5.1%), dizziness (6.3% vs 1.3%), fatigue 13.9% vs 5.1% and somnolence (6.3% vs 0%). Note: orvepitant was taken in the morning in this study.

Conclusions

- Orvepitant 30 mg once daily was effective in reducing the burden of cough in patients with RUCC
- The improvements in patient reported outcomes were clinically relevant and statistically significant in the full analysis set, and greater in patients with higher cough frequency at baseline
- Clear improvements in cough frequency were also shown in the higher frequency cough group, confirming similar observations in other studies[4,6]. Efficacy was not shown in lower cough frequency subjects due to greater variance in cough frequency in this group.
- Orvepitant was well tolerated with no safety concerns at any dose. It will be dosed in the evening in future studies.