

**Neurokinin 3 Receptor Antagonism as a Novel Treatment for Menopausal
Hot Flushes (REC 15/LO/1481; EudraCT 2015-001553-32)**

Final report

30/04/2018

This phase 2, randomised, double-blind, placebo-controlled, crossover trial assessed the effectiveness of an oral neurokinin 3 receptor antagonist (MLE4901) on menopausal hot flushes. Sixty-eight women were screened in a single-centre, of which 37 were randomised and included in an ITT analysis. Twenty-eight participants (aged 49-62yrs, experiencing ≥ 7 hot flushes/24h some of which were reported as bothersome or severe), completed the trial, and were included in a Per-Protocol analysis. They received 4 weeks of MLE4901 and placebo in random order separated by a washout period. Primary outcome was total number of hot flushes during the final week of both treatment periods.

The primary outcome was achieved. MLE4901 significantly reduced the total weekly number of hot flushes by 45% compared to placebo (Intention-to-treat: adjusted means: placebo 49.01 (CI: 40.81-58.56), MLE4901 19.35 (CI: 15.99-23.42), $p < 0.0001$). MLE4901 also significantly reduced weekly hot flush severity, bother, and interference compared to placebo by 41% ($p < 0.0001$), 45% ($p < 0.0001$), and 58% ($p < 0.0001$) respectively. Treatment was well tolerated. Three participants developed an asymptomatic transaminase rise (4.5-5.9x upper limit of normal) with a normal bilirubin 28 days after starting MLE4901, which normalised within 90 days.

Achievement of project objectives:

- Primary outcome achieved
- Potential new therapeutic identified for a significant unmet clinical need

- Discussions started with industrial partners regarding downstream processing
- Significant media interest (two separate press releases; one in 2017 and one in 2018 coinciding with publication of the two manuscripts) - best reflected by our high Altmetric score of 313 (as of 07/05/2017 (paper released Lancet Online 03/04/2017)), which is in the top 5% of all research outputs ever tracked by Altmetric, and 19th out of 396 outputs of similar age published in The Lancet. Covered by almost all of the British National Newspapers, some radio programmes such as BBC Radio 4 Woman's Hour, as well as social media, and some international news outlets. Similar media response to the second press release achieving global coverage with the total audience covered exceeding five million. We continue to receive invites from media companies who are interested in covering the trial within their programmes, and are therefore continuing to ensure that the findings from our research are being disseminated to a wide audience, and are publicly available.
- PPI video of results made and uploaded on Imperial College and Imperial trust website <https://vimeo.com/242031387>

Publications directly arising from this clinical trial:

- Prague JK, Roberts RE, Comninou AN, Clarke S, Jayasena CN, Nash Z, Doyle C, Papadopoulou DA, Bloom SR, Mohideen P, Panay N, Hunter MS, Veldhuis JD, Webber LC, Huson L, Dhillon WS. (2017) *Neurokinin 3 receptor antagonism as a novel treatment for menopausal hot flashes: a phase 2, randomised, double-blind, placebo-controlled trial*. Lancet 389: 1809-1820 [Epub 2017, Apr 3]
- Prague JK, Roberts RE, Comninou AN, Clarke S, Jayasena CN, Mohideen P, Lin VH, Stern TP, Panay N, Hunter MS, Webber LC, Dhillon WS. (2018) *Neurokinin 3 receptor antagonism rapidly improves vasomotor symptoms with sustained duration of action*. Menopause Mar 12. doi: 10.1097/GME.0000000000001090. [Epub ahead of print]

Two other manuscripts are also being prepared for submission to international peer-reviewed journals

Presentations arising from this clinical trial:

- ENDO. Chicago, 2018 Plenary lecture given by Prof Waljit Dhillon (*Title: Kisspeptin/Neurokinin B Pathways: Regulating Emotion and Treatment of Menopausal*

Symptoms)

- The Society for Endocrinology Annual Conference. Harrogate, 2017 (*Title: Neurokinin 3 receptor antagonism: a highly effective, novel treatment for menopausal hot flushes with rapid onset. Authors: JK Prague et al.*)
- North American Menopause Society Annual Conference. Philadelphia, 2017 (*Title: Neurokinin 3 receptor antagonism for menopausal hot flushes*)
- The British Menopause Society Annual Conference. Coventry, 2017 (*Title: Neurokinin 3 receptor antagonism: a highly effective, novel treatment for menopausal hot flushes with rapid onset. Authors: JK Prague et al.*)
- European Endocrine Society Conference. Lisbon, 2017. Lecture given by Prof Waljit Dhillon (*Title: Kisspeptin and Neurokinin B*)
- The European Menopause and Andropause Society Conference. Amsterdam, 2017 (*Title: Neurokinin 3 receptor antagonism: a highly effective, novel treatment for menopausal hot flushes with rapid onset. Authors: JK Prague et al.*)
- ENDO. Florida, 2017 (*Title: Neurokinin 3 receptor antagonism as a novel treatment for menopausal hot flushes: a phase 2, randomised, double-blind, placebo-controlled trial. Authors: JK Prague et al.*)

Dissemination of the results to the participants:

All the participants were invited to an end of study 'tea party' to thank them for participating in the trial and to inform them of the results. Subsequent updates regarding the results of further analyses were relayed in person when they attended for the additional study visit as part of the substantial amendment. Further updates have been relayed by email from the study coordinator.