DEAL WATCH

Neurokinin 3 receptor antagonist revival heats up with Astellas acquisition

Japan's Astellas Pharma has announced that it will acquire the Belgian biotech Ogeda for up to €800 million, including milestone payments (FIG. 1). Ogeda's sole clinical asset, fezolinetant, is a small-molecule inhibitor of the neurokinin 3 receptor (NK3R), for which the company reported promising results from a phase IIa trial for the treatment of menopausal hot flushes in January 2017.

Hot flushes affect 70% of menopausal women, 10% of whom report them as intolerable. Although hormone replacement, the leading therapy for these individuals, can be effective, it is contraindicated in many women for safety reasons. Alternative treatments, including gabapentin and antidepressants, have substantial side-effects. Hormone-related hot flushes can also affect people undergoing treatment for breast or prostate cancer.

In the 1990s and early 2000s, numerous pharmaceutical companies developed small-molecule antagonists of NK3R as a potential treatment for schizophrenia, as NK3R and its main ligand, neurokinin B (NKB), were thought to have a role in neurotransmitter crosstalk. The tide turned following clinical trial failures due to lack of efficacy, and most of these compounds were shelved, sold or spun out into smaller companies.

Interest in NK3R was renewed by its identification as a key mediator of oestrogen-mediated thermoregulation by Naomi Rance, a professor of pathology at the University of Arizona, in Tucson, USA. For more than 25 years, her research has focused on the physiological function of a subset of neurons that she found to be altered in the hypothalami of post-menopausal women. "I was really trying to work out the basic biological circuit for these neurons to influence reproduction and thermoregulation," she explains. She showed that hypothalamic neurons that express kisspeptin, NKB and dynorphin (KNDy neurons) could be involved in flushing caused by oestrogen deficiency. KNDy neurons project into thermoregulatory areas in the preoptic hypothalamus and facilitate skin vasodilation, a cardinal feature of the menopausal flush (*Proc. Natl Acad. Sci. USA*, **109**, 19846–19851; 2012).

At the same time, Waljit Dhillo, a professor and endocrinologist at Imperial College London, UK, had been investigating the role of NKB in reproductive hormone release. NK3R is also involved in the release of gonadotropin-releasing hormone, which constitutes the initial step in the hypothalamic–pituitary–gonadal axis of hormonal control. Although NKB didn't stimulate hormone release in adults, it did induce some flushing. "It was one line in that paper, but we put two and two together when we heard [Rance] talk at a meeting in 2012," he said. He then showed that injecting pre-menopausal women with NKB could induce hot flushes (*Sci. Rep.* **5**, 8466; 2015), solidifying the role of NKB and NK3R in this phenomenon in humans.

"If neurokinin B is the cause of the menopausal flushing then a neurokinin B receptor blocker could be a new and effective drug to treat this condition," Dhillo reasoned. Knowing that many companies had NK3R antagonists in need of an indication, Dhillo approached AstraZeneca, who agreed to provide their compound. Dhillo led a phase II trial that examined this NK3R antagonist — AZD4901, which was outlicensed to Millendo Therapeutics partway through the trial and is now known as MLE4901 — in post-menopausal women with severe or bothersome hot flushes (*Lancet* **389**, 1809–1820; 2017). MLE4901 significantly reduced the total weekly number of hot flushes by 73% compared with baseline and by 45% compared with placebo. "It's almost unbelievable how efficacious it is — I wouldn't have expected one single agent to have such a big effect," says Dhillo.

Promising results were also reported in Ogeda's phase II double-blind, placebo-controlled trial; fezolinetant reduced the frequency (93% reduction versus 38% reduction for placebo after 12 weeks) and severity (70% reduction versus 23% reduction for placebo after 12 weeks) of moderate-to-severe hot flushes after both 4 and 12 weeks of twice-daily oral treatment.

"Studies to investigate menopausal flushing have to be done very carefully, and Ogeda also did their study with a robust protocol," Dhillo highlights, "because you get a big placebo effect in this condition."

A third NK3R inhibitor, NT-814, which is owned by NeRRe (a GlaxoSmithKline spin-out), is in an ongoing phase II trial of NT-814 for hot flushes (NCT02865538).

NK3R inhibitors could be useful in other hormone-related conditions: MLE4901 (NCT02865915) and fezolinetant are being examined in women with polycystic ovary syndrome, and fezolinetant is also being investigated as a treatment for uterine fibroids and endometriosis.

Interestingly, Rance has also shown that KNDy neurons are essential for oestrogen-mediated suppression of weight gain (*Endocrinology* **153**, 2800–2812; 2012). Ogeda has also been investigating NK3R in weight gain — at ENDO 2017, they presented results in which fezolinetant suppressed weight gain in ovarectomized rats and cynomolgus monkeys fed a high fat diet. So NK3R inhibition could control both hot flushes and weight gain commonly associated with menopause.

Dhillo notes that having access to shelved drugs was key to accelerating the research. "If we were starting 2 years ago with making a new molecule we'd be here 10 years on," he says. Rance emphasizes the importance of basic research. "The more we know about basic physiology and neuroscience, the more likely it is that we will have some way to modulate it: we had to understand what causes hot flushes before figuring out a way to treat them," she says.

Megan Cully

FURTHER INFORMATION

Fezolinetant phase IIa trial results: https://www.ogeda.com/news/ogeda-announces-positive-data-from-phase-iia-trial-of-fezolinetant-esn364-in-the-treatment-of-menopausal-hot-flashes

ENDO 2017 fezolinetant abstract: https://plan.core-apps.com/tristar_endo17/abstract/f7e437ee5c2d999047a0315444c69d17

NCT02865538: https://clinicaltrials.gov/ct2/show/NCT02865538

NCT02865915: https://clinicaltrials.gov/ct2/show/NCT02865915

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Astellas Pharma to acquire Ogeda SA — Date announced: 3 April 2017

Deal type: acquisition	**Value: up to €800 million**
• Acquiring company: Astellas Pharma • Acquired company: Ogeda SA	• €500 million upfront • Up to €300 million additional in milestone payments

Asset characteristics
• Ogeda's clinical compound, fezolinetant, is a small-molecule inhibitor of the neurokinin 3 receptor (NK3R) that showed efficacy in a phase IIa trial for hot flushes in menopausal women. Two other NK3R antagonists — MLE4901 and NT-814 — are being investigated for the same indication

Figure 1 | **Deal snapshot.**