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## Drug developers reboot anti-NGF pain programmes

Pfizer, Eli Lilly, Janssen and Regeneron are advancing a promising class of analgesic drugs, hoping to put concerns around autonomic dysfunction and joint destruction behind them.

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US regulators released Pfizer and Eli Lilly's tanezumab from clinical hold in March this year, raising hopes for the nerve growth factor (NGF) inhibitors that were once considered to have mega-blockbuster potential. The US Food and Drug Administration (FDA)'s hold was implemented in 2010 after an increased incidence of joint destruction was observed in patients on this class of drugs, but an action plan was established to address this red flag in 2012. The subsequent delay has largely been due to preclinical studies that suggested that the drugs could damage the autonomic nervous system. Pfizer, Lilly, Janssen, Regeneron and others

hope that Phase III trials will now put both safety concerns fully to rest.

"We are very supportive of the FDA and their careful assessment of safety," says Catherine Stehman-Breen, Vice President of Global Development at Regeneron, which is developing the anti-NGF fasinumab. "No one knew quite what to make of these preclinical findings, and I think [the hold] was a very reasonable and appropriate measure for the FDA to take."

Neither the FDA nor the anti-NGF drug developers have disclosed detailed reasoning for the concerns about effects on the autonomic nervous system, which regulates automatic body processes such as heart rate, blood pressure, breathing and digestion. Last year, however,

Regeneron reported that the fears had been triggered by "adverse changes in the sympathetic nervous systems of mature rats and monkeys in neurohistologic studies" of two NGF-specific antibodies that were being developed by other companies. "The FDA raised the question of whether there might be a clinical risk of continual loss of cells and resultant neurological deficits with repeated dosing," they wrote (*Pain* **155**, 1245–1252; 2014).

Pfizer told *Nature Reviews Drug Discovery* that the FDA lifted the hold on their tanezumab in March after seeing "a robust body of nonclinical data" demonstrating that "tanezumab administration does not cause neuron cell loss or death in the sympathetic nervous system". "Tanezumab

treatment does result in a reduction in size of some neurons,” wrote a company spokesman, but “the effect does not progress with chronic treatment, is reversible with treatment cessation, and is not believed to have functional consequence or significance”.

For some, the timing of this delay begs an explanation. Anti-NGFs have been known to have morphological effects on the sympathetic nervous system for decades. Rita Levi-Montalcini and colleagues started showing that the NGF pathway is critical for the development and maintenance of the sympathetic nervous system in the 1960s, and she won a Nobel Prize for this work with Stanley Cohen in 1986. Moreover, by the time the clinical hold was put in place, drug companies had extensive safety data from their products. Pfizer alone had tested its anti-NGF in thousands of patients in Phase III trials and had not reported any increased risk of adverse events associated with autonomic dysfunction, such as increased heart rate, blood pressure or sweating.

“Why that hold was considered rational was completely beyond my ability to understand,” says David Cornblath, a neurologist at John Hopkins, in Baltimore, Maryland, USA, who has acted as a consultant for companies in the anti-NGF space. “There may be other information that the FDA has access to, but based on what I know I can’t imagine what that reason might be.”

Although some adverse events associated with autonomic dysfunction can be hard to pick up in clinical trials, others — like orthostatic hypotension, leading to dizziness — are not subtle and could show up on adverse-event reports. And the high unmet need of osteoarthritis patients who suffer from severe pain and deal with the risks of approved analgesics further complicate the matter. “Even if you found that there was a tiny statistical difference in drug versus placebo on whatever your autonomic dysfunction end point was, the available safety data already demonstrate the irrelevance of a small human safety signal,” he says. “Not everything that we detect is relevant.”

“I’m glad the hold has been finally lifted,” says Cornblath.

The FDA declined to comment on the autonomic dysfunction safety concerns.

### Mitigating strategies

Although Pfizer and its partner Lilly are as yet the only firms to get the full regulatory green light for their drugs, Janssen and Regeneron are also gearing up their anti-NGF engines. Janssen has relisted four Phase III trials with its fulranumab on Clinicaltrials.gov. The FDA also downscaled a clinical hold on Regeneron’s

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fasinumab earlier this year, allowing trials with up to 16 weeks of exposure. Regeneron anticipates the hold will be fully lifted by the end of 2015. Several other companies, including AstraZeneca, AbbVie and Teva, were also working on NGF-specific antibodies before the 2010 hold. Osteoarthritis pain remains the prize indication.

“We think this is an area of huge unmet medical need,” says Stehman-Breen. “We know that physicians are excited that these programmes are getting back underway.”

The holds have taken a toll, however, and considerable clinical data are still needed to secure approval. “The Phase III programmes have to be repeated,” cautions Colin Miller, a consultant at Alacrita Consulting who has worked on the anti-NGFs.

Drug developers will have to include several mitigation strategies in these new Phase III programmes just to handle the joint destruction safety signal. At a 2012 FDA advisory committee, experts heard how 245 patients on anti-NGFs experienced joint destruction that was unlikely to have occurred as a result of the natural progression of their osteoarthritis, compared with only 40 patients in the placebo arms of the trials (*Nature Rev. Drug Discov.* **11**, 337–338; 2012). As a result, the panel recommended that patients need more thorough radiographic assessment at enrolment, adding to the cost and increasing the enrolment-screening failure rates of the trials. “Historically, osteoarthritis trials have recruited patients very easily. Now, you are going to have to screen them all with knee, hip and shoulder radiographs and screen out patients who might have underlying pathology,” says Miller. The radiological screening and safety assessments alone will add an extra US\$100 million–\$200 million to the cost of each programme, he estimates.

At issue is whether trialists observed joint destruction in earlier trials because some patients had a pre-existing condition and overused their joints because of the desired analgesic effect of the drugs, or because the drugs themselves had a direct detrimental pharmacological effect. “That’s a big question,” says Miller. By ruling out pre-existing conditions and by establishing a better baseline of joint health, investigators hope to generate an answer.

The two possibilities may not be mutually exclusive, cautions Luigi Manni, a neurobiologist at the Institute of Translational Pharmacology at the National Research Council of Italy. He also points out that the NGF receptor is present in bone tissue and that exogenous NGF has been shown to speed up fracture healing. “You can imagine a process in which you have a lot of inflammation, and the bone is suffering, and when you block NGF you are blocking not only the pain system that is conveying information about the trauma but also all the healing and remodelling processes that would be taking place,” he explains. “This would be a serious problem.”

One solution could be to better tune the dosing of the anti-NGFs to minimize adverse events. A systematic review of the NGF-specific antibodies recently reported that lower doses of antibody (2.5 mg and 5 mg) are associated with fewer adverse events that led to study withdrawal than the higher (10 mg) doses (*Osteoarthritis and Cartilage* **23**, S8–S17; 2015). The question could become whether these lower doses will offer enough analgesic efficacy over existing options.

All anti-NGF drug developers will now also have to look prospectively for adverse events that are linked with the autonomic nervous system, adds Stehman-Breen. “But that is fairly standard for any clinical trial programme. As you learn more about the drug, you add more adverse events to your list of adverse events of interest and carefully assess those prospectively.”

Trials might also exclude patients with increased risk of autonomic dysfunction, such as those with diabetes. But given the lack of safety signals to date, adds Stehman-Breen, this wouldn’t necessarily mean that in clinical practice these patients would be ineligible for anti-NGF therapies.

The financial prospects for the anti-NGF class have also been battered by the protracted delay. Prior to the 2010 hold, analysts forecasted that anti-NGFs would hit sales of \$11 billion by 2023. In 2014, a revised estimate by Decision Resources slashed combined sales of tanezumab and fulranumab to just \$5.4 billion by 2023. The additional safety questions might shrink sales expectations further still. Natalie Taylor, an analyst at Decision Resources, says that autonomic safety concerns could call into question the prospects for the anti-NGFs in neuropathic pain indications. But osteoarthritic pain is so common, she adds, that even a 0.25% market share in this indication could still turn the anti-NGFs into blockbuster drugs.