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Therapeutic focus - Return of anti-NGF class gets FDA panel's backing

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An FDA expert panel's support for resumption of research on pain-killing anti-nerve growth factor (NGF) antibodies should presage a new round of clinical work on the promising class. Data presented at the advisory committee's meeting yesterday identified factors involved in joint destruction including simultaneous use of NSAIDs and a history of rapidly progressing osteoarthritis.

This should be good news for Pfizer, Abbott Laboratories and Regeneron, which have the most-advanced candidates in the pipeline (see table). Despite drugmakers desire to push on with registration studies, it is not clear that the regulator will allow this to happen, meaning all the compounds are years from the market.

Pain blocker

Nerve growth factor NGF is essential for the survival of developing neurons. However, it has been found to be elevated in patients suffering acute and long-term pain. Thus, a blockade of NGF is a promising area of research in treating patients with chronic pain, osteoarthritis in particular, who are not responsive to conventional pain-killers.

Last year, the FDA took the extraordinary step of suspending all work in the anti-NGF antibody field when an imbalance in osteonecrosis leading to joint replacement was reported with use of the drugs – a clinical hold began with Pfizer's tanezumab but then was extended to Johnson & Johnson's fulranumab and Regeneron and Sanofi's SAR164877/REGN475, the most-advanced drugs in the class (*Event - Adcom will take broad look at anti-NGF antibodies, July 25, 2011*).

An adjudicated review has categorised most of the originally reported cases of osteonecrosis as rapidly progressing arthritis, still a concern for regulators in that joint replacement is necessary; however, in many of the cases it was considered part of the normal progression of arthritis and not necessarily related to treatment with an anti-NGF agent.

A strong link was seen with combination therapy using NSAIDs, along with higher doses of the antibodies and advanced disease at the trial's baseline. To mitigate this the three companies proposed clinical strategies to reduce those risks, along with exclusion of patients who have adequate relief on conventional pain relievers and discontinuation of non-responsive patients.

Thus the 21-0 vote to allow the companies to restart the programmes in arthritis and 20-1 in other painful conditions in which there are no agents with an analgesic effect, which should offer agency officials the validation they need to lift the clinical holds if they decide to do so. It is not clear when that decision will be made.

Anti-NGF pipeline for osteoarthritis pain					
Status	**Product**	**Generic Name**	**Company**	**Originator**	**Trial ID Completed**
Suspended Phase III	PF-4383119	tanezumab	Pfizer	Genentech/XOMA	NCT00744471 NCT00733902 NCT00830063 NCT00863304
Suspended Phase II	AMG 403/JNJ-42160443	fulranumab	Johnson & Johnson	Amgen	-
	SAR164877/REGN475	-	Sanofi/Regeneron Pharmaceuticals	Regeneron Pharmaceuticals	NCT00944892
Phase I	PG110	-	Abbott Laboratories	Lay Line Genomics/PanGenetics	NCT00941746
Suspended Phase I	MEDI-578	-	AstraZeneca	AstraZeneca	-

The story so far

Pfizer has completed four phase III trials of tanezumab, also known as PF-4383119, in 3,000 patients with hip or knee arthritis, but was forced to terminate nine other trials. Two phase II trials in cancer patients with bone metastases are recruiting.

J&J cancelled six trials of fulranumab, known variously as AMG 403 and JNJ-42160443, as an-add on in arthritis and low-back pain, along with monotherapy trials in neuralgia, bladder pain and diabetic neuropathy. A cancer pain trial is recruiting.

Regeneron and Sanofi had completed trials of REGN475 in osteoarthritis and sciatic pain that had enrolled more than 300 patients, but another four in pain related to pancreatitis, vertebral fractures and burns had to be ceased.

Should the FDA clear the three compounds for clinical research again, the companies will need to assess their programmes for the balance of risks and benefits and knowledge of the safety signals; it would not be surprising to see a narrowing of trials to arthritis and chronic back pain, along with the continuing work in cancer pain, given the worries about joint destruction.

If anybody should be happy about the vote, it should be Abbott Laboratories, which paid a whopping $170m to buy phase I PG110 from private Dutch biotech PanGenetics in late 2009, only months before news started emerging about the bone-related safety signal (*PanGenetics cashes in on Abbott's early stage bet, November 13, 2009*). Whilst any work has been delayed by nearly two years, it at least makes the decision to buy the humanised antibody outright look a little less imprudent, rather than the less risky strategies of licensing or optioning it. A 56-patient phase I safety and tolerability trial of PG110 in osteoarthritis patients wrapped up early last year.

AstraZeneca has also ceased work on MEDI-578 in a phase I osteoarthritis trial. As with Abbott Laboratories' purachase of PG110, success with MEDI-578 would help justify Astra's disappointing acquisition of MedImmune. No doubt both companies are watching regulatory developments closely to determine whether to restart their early-stage clinical programmes.

Although the FDA's hold on the class was a big blow, success may yet emerge for the anti-NGF antibody class. The answer lies several years in the future, and most likely in a narrower population whose pain cannot be relieved with existing treatments.