Evaluate Vantage

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EULAR Preview - Pfizer's tofacitinib to take centre stage

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The latest swathe of data from Pfizer on its novel oral rheumatoid arthritis therapy, tofacitinib, are hotly awaited at next week's European League against Rheumatism meeting, with its safety profile likely to take centre stage.

Interest is being piqued because the pill is not only the most important pipeline product for the world's biggest drug maker, it could also radically shake up an RA market dominated by injected therapies. Other novel RA therapies from Eli Lilly and AstraZeneca and a new gout treatment from Ardea will also be featuring at the conference. But it seems likely tofacitinib will hog the limelight as the medical and financial communities attempt to assess exactly how transformative this new pill could be.

Top line clarification

Pfizer will be presenting data from one of its five pivotal tofacitinib studies, called Oral Sync. This aimed to recruit 750 patients with moderate to severe RA and who had failed to respond to one disease modifying anti-rheumatic (DMARD) – for example methotrexate or an anti-TNF agent like Enbrel. While still taking the DMARD, patients were also given either tofacitinib or a placebo pill.

Headline results released in March declared the trial a success, showing significant reduction in the signs and symptoms of RA on various measures at six months, over placebo (*Pfizer's biggest pipeline drug needs to keep performing, March 4, 2011*).

However, although at the time Pfizer said no new safety signal was detected the company was forced to release a clarifying statement after the abstract for the study was released last month.

The company confirmed that four deaths were reported in the tofacitinib arms of the study, three of which were determined by the investigators not to be study drug related. These involved one case of brain injury following trauma 22 days after discontinuation of study drug; one case of worsening of RA 42 days after discontinuation of study drug; and one case of acute heart failure. One case of respiratory failure was reported by the investigator as study drug related.

Pfizer pointed out that because the initial randomisation design of the study includes only one-fifth of the patients on placebo, and because the placebo patients are converted to active arms beginning as early as three months into the study, the majority of adverse events would be expected to occur in patients on active treatment. It added that the mortality rate from all causes across the tofacitinib RA development program is within the range of rates reported for biologic therapies for RA.

However these deaths will be a key focus when the data are presented, particularly the case of respiratory failure. The study has a late-breaker oral session slot on Friday May 27, at 4:20pm London time.

Safety signals

News of the deaths caused Pfizer's shares to drop 3% on the day to $19.79 but the stock has more than recovered since; in early trade today shares touched $21.14, more than a three-year high.

Growing hopes for tofacitinib have contributed to a strong recovery this year for Pfizer – the stock has advanced 20% this year. Analysts believe the drug could be generating $1.56bn by 2016, a figure that has surged 53% so far this year, according to archived consensus forecasts from *EvaluatePharma*.

Few financial analysts believe these deaths, and others reported in previous studies, have flagged any safety signal that might derail tofacitinib. Still, the drug is already known to raise LDL – another trial that will be of interest at EULAR tested tofacitinib in combination with Lipitor.

Not all analysts are convinced the LDL impact will escape intense FDA scrutiny, in the light of the withdrawals of Vioxx and Avandia, both withdrawn amid much furore due to cardiovascular side effects.

Other known side effects are neutropaenia and anaemia, all are seen as easily identifiable and reversible. What is still unknown is whether the drug increases the risk of serious infection – should this signal emerge it will cause considerable concern.

More data needed

The safer the drug the more likely it will be used in earlier stages of diseases, and this remains the big unknown for tofacitinib – ending up as a drug of last resort will clearly hit commercial potential. Safety signals could also delay approval – Pfizer plans to file in the second half of this year.

A lot of data are still needed to fully characterise tofacitinib's benefits and risks – the presentations at EULAR will be an important start but the American College of Rheumatology (ACR) meeting in November will yield even more data.

Here, full data from three more trials will be presented - Oral Scan, Oral Standard and Oral Step. Pfizer has presented positive top line data from all these studies but, as always, the devil will be in the detail. Details from Oral Standard, which pits the drug against Abbott Laboratories' Humira, will be of particular interest. Pfizer has so far only said the drug beat placebo and has not revealed any relative benefit versus the $6.5bn anti-TNF antibody, although admittedly the trial was not designed for a statistical comparison of the two agents. Similar efficacy is expected.

Other agents

Other oral RA agents with data at EULAR include AstraZeneca and Rigel's fostamatinib, a SYK inhibitor that has recently moved into phase III. Fresh phase II data will be presented and closely scrutinised, as the agent could represent a real competitive threat to Pfizer and tofacitinib a few years down the road.

Phase II data are also due on Galapagos' contribution to the oral field, GLPG0259, a novel MAPKAPK5 inhibitor which was abandoned last month, and pre-clinical data on a follow on candidate, GLPG0634, a combined JAK/TYK2 inhibitor that will hopefully take its place (*Galapagos' punishment for loss of RA lead looks harsh, April 15, 2011*).

Other novel RA drugs that will also be scrutinised at EULAR include Eli Lilly's B-cell activating factor inhibitor, tabalumab. Phase II data in patients on methotrexate and TNF failures will be presented. The antibody has a similar mechanism of action to Human Genome Science's newly approved lupus therapy, Benlysta, which failed in RA, so Lilly's progress will be of interest.

And much earlier stage, Myrexis will report pre-clinical findings from its oral anti-interferon candidate, MPI-0485520, in collagen-induced arthritis.

Gout developments

Outside of RA, phase IIb data from Ardea's gout therapy, RDEA594, will also be of interest following positive top-line results in January, as well as results from some earlier stage studies. Known generically as lesinurad, the URAT1 inhibitor is being prepared for phase III studies and is the company's lead product, with big potential seen as a combination therapy with allopurinol in a second line setting.

Also in gout, BioCryst Pharmaceuticals will present early stage data from its next next generation purine nucleoside phosphorylase (PNP) inhibitor, BCX4208.

Meanwhile Savient will present long term safety data on Krystexxa, its newly approved gout therapy, the launch of which is causing some concern for investors (*Tough quarter for new product launches by small pharma groups, May 11, 2011*).

Drug	Trial ID	Trial name
Tofacitinib	NCT00847613	Oral Scan
Tofacitinib	NCT00960440	Oral Step
Tofacitinib	NCT00856544	Oral Sync
Tofacitinib	NCT01039688	Oral Start
Tofacitinib	NCT00814307	Oral Solo
Tofacitinib	NCT00853385	Oral Standard