ESC - Eisai and Relypsa contribute good looking mid-stage candidates

Whilst many eyes at the European Society of Cardiology (ESC) 2010 congress in Stockholm were following the big name prospects of Xarelto and apixaban, Eisai and Relypsa’s phase II candidates generated some promising safety, tolerability and efficacy data for the middle of the pack (Preview - ESC to throw up more than just the hot topics, August 26, 2010).

Eisai’s E5555 is hoping to find its own niche in the anti-thrombotics space, where stiff competition is developing, with a mechanism of action not well-explored. Relypsa’s RLY5016, already having its own unique market in hyperkalaemia, is trying to show a significant level of efficacy in this rare potassium disorder including in the alleviation of drug-induced hyperkalaemia.

Eisai off to a good start

It is too early to tell if Eisai’s E5555, a drug for acute coronary syndrome (ACS) working by the novel mechanism of protease-activated receptor 1 (PAR-1) inhibition, will be able to stand up in an anti-thrombotic market that is shaping up to be fiercely competitive (Therapeutic focus - Anti-thrombotics face a period of change, July 26, 2010).

Eisai reported mid-stage results at the ESC for its phase II candidate E5555 from the J-Lancelot trials, in Japanese patients with ACS and stable coronary artery disease (CAD). Safety and tolerability were assessed in the first study, with a second to evaluate efficacy in stopping major adverse cardiac events (MACE; cardiovascular-related death, myocardial infarction, stroke and recurrent ischemia) and platelet aggregation.

A major safety issue with these sorts of drugs is the incidence of excessive bleeding. Although, as could be predicted, there was a dose-dependent increase in the minimum amount of bleeding, Eisai’s candidate caused no increase in clinically significant bleeding compared to placebo. And bleeding did not increase even when the drug was administered as an addition to standard care – aspirin and thienopyridine antiplatelet therapy. The drug was also well-tolerated.

It seems also that PAR-1 inhibition may be a very effective means of stopping platelet aggregation, with 90% mean inhibition at the 100 and 200 mg dose levels of E5555. And although principal investigator Professor Shinya Goto, Tokai University School of Medicine, conceded the studies were not big enough to show real efficacy in controlling MACE, nevertheless there was a lower incidence of events in the active groups compared with placebo.

Commenting on the findings, Prof Goto said: “From these results, PAR-1 receptor antagonism may be an attractive pathway in the treatment of atherothrombosis.”

Whilst showing itself to be promising target, it is not clear whether inhibition of the PAR-1 receptor represents a superior class of anti-thrombotic over those currently in development. Further, bigger studies will be needed to determine statistically significant results and Eisai has yet to reveal its plans for the drug.

Relypsa’s double-edged hyperkalaemia sword

Some significant phase IIb data did surface from trials of Relypsa’s RLY5016, a potassium binder for hyperkalaemia, a disorder of elevated serum potassium. The drug was tested in PEARL-HF, a randomised, double-blind, placebo-controlled study in 104 heart failure patients with chronic kidney disease.

Overall, RLY5016 reduced hyperkalaemia by 25%, compared with only 7% in the placebo group.

Of particular note, RLY5016 alleviated hyperkalaemia induced by aldosterone antagonists. These are commonly used, with good effect, to treat chronic kidney disease. Hyperkalaemia, and its resulting risk of developing heart arrhythmia, is their major limiting side effect.
This unique activity could potentially accelerate development of Relypsa’s drug. Chronic kidney disease sufferers in the later stages of disease will likely develop hyperkalaemia as a result of renal inability to excrete potassium, so patients are at risk of hyperkalaemia from both kidney disease, and the standard care used to treat it, such as spironolactone and eplerenone.

The trial steering committee chairman, Professor Bertram Pitt, University of Michigan School of Medicine, described this particular finding as “very significant”. Removing a hyperkalaemia risk altogether would open treatment doors in both the chronic kidney disease and arrhythmia arenas.

This added efficacy could serve Relypsa well in its hunt for a partner, which it has said it will seek out “for certain territories and indications”.

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