Isis snags Bayer in quest for anticoagulant Holy Grail

Robin Davison

Large share price gains for biotechs on licensing deals with big pharma have become so common that the most notable aspect of yesterday’s tie-up in which Bayer obtained rights to Isis’s Factor XI inhibitor ISIS-FXIRx was the muted stock market response.

Ordinarily, a lucrative deal with such a major player would justify a larger market reaction than the 2.4% rise seen by Isis yesterday. But the stock market appears to see ISIS-FXIRx as a niche product in market well served by Factor Xa inhibitors. This coolness is all the more surprising given that the project has been discussed as potentially being the Holy Grail of antithrombotic therapy: an effective anticoagulant with no increased risk of bleeding.

Investors added just $170m to Isis’ $7bn market capitalisation – little more than the value of the up-front and the near-term milestone payment. Nevertheless, Isis has found a strong partner and obtained a $100m signing fee with a further $55m due on completion of a phase II study in patients with compromised kidney function.

It will also receive an additional $220m in development milestones and tiered 20-30% royalties on gross margins of ISIS-FXIRx. On completion of Isis’s ongoing activities Bayer will assume all global clinical development, regulatory and commercialisation responsibilities for ISIS-FXIRx.

Avoiding bleeds

The data that attracted Bayer were presented at ASH last year and simultaneously published in the New England Journal of Medicine. These were from a 293-patient phase II study for the prevention of venous thrombosis (VTE) in patients undergoing total knee replacement surgery.

The study showed that patients treated with the higher 300mg dose of ISIS-FXIRx had a sevenfold lower incidence of VTE compared with enoxaparin – a statistically significant 4.2% vs 30.4%. Patients treated with a 200mg dose of ISIS-FXIRx had comparable incidence of VTE to enoxaparin-treated patients: 26.9% vs 30.4% respectively.

Meanwhile, the proportion of patients with major or clinically relevant non-major bleeds was numerically lower but not significantly so, at 2.6% and 2.8% for ISIS-FXIRx 300mg and 200mg respectively, versus 8.3% for enoxaparin. This is important since the prevailing wisdom has been that improvements in reducing VTE can only be achieved at the expense of higher rates of bleeds.

Patients in the study received subcutaneous ISIS-FXIRx on seven occasions in the six weeks before surgery and twice, at six hours and three days, after surgery. Those in the enoxaparin group received 40mg of enoxaparin the evening before surgery, and once daily thereafter for at least eight days.

The study allowed direct comparison with enoxaparin, but also suggests ISIS-FXIRx has lower rates of VTE than were seen in trials of the oral factor Xa inhibitors in the same setting of knee replacement surgery.

This might ordinarily mark out ISIS-FXIRx as having the potential to be best in class – but the project’s slow onset of action, the complexity of its dosing schedule and its non-oral route of administration will likely bar it from most acute settings.

Nevertheless, it is attractive for a number of niche indications. Bayer plans to evaluate ISIS-FXIRx initially in patients for whom currently available anticoagulants may not be used, including those with a high-risk of bleeding due to multiple co-morbidities.

One such setting could be patients with atrial fibrillation and end-stage renal disease, hence the current study. These patients are at high risk of stroke, but are rarely treated with anticoagulants because of the risk of bleeding.

Bayer will ultimately determine what indications to pursue; it already has a substantial commercial interest in
the anti-thrombotic market through its joint ownership of Xarelto with Johnson & Johnson. This is the largest-selling product in a therapy class that EvaluatePharma consensus data suggest will achieve $19bn in sales in 2020. Xarelto principally competes with Bristol-Myers Squibb’s Eliquis, Boehringer Ingelheim’s Pradaxa and Sanofi’s Lovenox.

Sellside reaction to the Isis deal has been low-key perhaps because of the uncertainty over the specific indications that will be pursued. Quite how Bayer achieves this and optimises ISIS-FXIRx’s potential without affecting Xarelto will be an interesting dilemma for analysts to ponder over for a few years to come.

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