BIOBUSINESS BRIEFS

AstraZeneca bets on FibroGen's anaemia drug

AstraZeneca has committed US\$815 million to co-develop and co-commercialize FibroGen's anaemia compound FG-4592 in the United States and China, including an upfront payment of \$350 million. FG-4592, a small-molecule inhibitor of hypoxia-inducible factor prolyl hydroxylase (HIF-PH), is in Phase III trials for the treatment of anaemia in patients with chronic kidney disease (CKD) and could become a first-in-class treatment option.

More than 80% of patients with CKD suffer from anaemia owing to decreased renal synthesis of erythropoietin (EPO). The decrease in red blood cell (RBC) production that ensues starves tissues of oxygen, leading to fatigue and other symptoms such as shortness of breath and palpitations. At present, treatment initially involves the oral or intravenous administration of iron, a vital constituent of the RBC's oxygen-carrying protein haemoglobin. If the desired levels of haemoglobin are not reached, then the second step is to administer erythropoiesis-stimulating agents (ESAs), which target the receptor for EPO to stimulate the production of RBCs. Several forms of recombinant EPO are effective and generally

well tolerated. Long-acting formulations, such as darbepoetin (Aranesp), also offer the advantage of less frequent dosing. However, the limitations of ESAs — their limited efficacy in patients with inflammation as well as their side effects, mainly thromboembolic events possibly related to high ESA dosage — have driven research into alternative approaches to mobilize the erythropoietic machinery.

Recent studies in anaemic patients with CKD at altitude have shown that these patients need lower doses of EPO and that they respond better to such treatment. These findings indicate that the body's response to high-altitude hypoxia involves a more efficient induction of erythropoiesis. HIF is an oxygen-sensitive transcription factor that mediates cell survival during hypoxic conditions by activating (among other factors) EPO and regulating iron mobilization and utilization. HIF activity is negatively regulated by HIF-PH, so by inhibiting this enzyme FG-4592 prevents the degradation of HIF and stimulates erythropoiesis.

"The advantages [of FG-4592] over a purely EPO-based treatment include changes in metabolism, particularly iron metabolism, that ideally should accompany erythropoiesis,

but that EPO alone does not efficiently induce," says Randall Johnson, a physiologist at the University of Cambridge, UK.

Furthermore, "by stimulating endogenous EPO, the plasma levels of EPO in patients treated with HIF-PH inhibitors will be very low in comparison with those treated with recombinant EPO, which could be important in reducing the side effects", says Francesco Locatelli, nephrologist and Scientific Director at Alessandro Manzoni Hospital, Lecco, Italy.

Potential limitations of this type of HIF-PH inhibitors include their selectivity. "Ideally, one would like a compound that only induces HIF-pathway genes directly relevant to erythropoiesis, and not genes such as VEGF-A [vascular endothelial growth factor A], for example, that might induce abnormal angiogenesis," says Johnson. Frequent oral administration could also be an issue for patient compliance, considering the very large number of pills that patients with CKD are prescribed, says Locatelli.

AstraZeneca is aiming to file for US regulatory approval in 2017 and plans to develop FG-4592 to treat additional anaemia indications. There are also other companies developing HIF-stabilizing drugs, including Akebia Therapeutics, which has a compound in Phase II trials. Although the initial focus has been on erythropoiesis, HIF modulators may also be useful for stimulating wound healing and collateral blood vessel growth in cardiovascular injury, treating inflammatory diseases such as colitis and regulating metabolic dysfunction. "There is clearly tremendous potential in this as a future arena for drug development," concludes Johnson.

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