GSK declines option on Exelixis's XL784 after Phase II results

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Jan. 22, 2008 - *PRLog* -- GlaxoSmithKline has decided not to exercise its option to license Exelixis's (San Francisco, California) kidney disease drug XL784 for further development and commercialisation. This follows the drug's failure to meet its primary endpoint in a Phase II trial in patients with albuminuria due to diabetic nephropathy.

Exelixis says it was not surprised by GSK's decision because the agreement between them gives GSK the option to develop and commercialise up to three out of nine candidates in Exelixis's product pipeline. GSK has already taken up an option to exclusively license the MET inhibitor XL880, currently in Phase II trials in patients with papillary renal cell carcinoma, gastric cancer, and head and neck cancer. Exelixis says the data being generated by other candidates made it unlikely that GSK would use one of its one or two remaining options for XL784.

Although the drug missed its primary endpoint, Exelixis says it was well tolerated and data from one subgroup were encouraging. The company does not intend to invest further in XL784's development itself, but will seek a partner with which to take it forward. Under the terms of the GSK deal, sales of any resulting products would be subject to a 3% royalty payment to GSK.

XL784 is a potent inhibitor of the ADAM-10 and MMP-2 metalloprotease enzymes, which play a role in the pathogenesis of diabetic nephropathy and renal fibrosis. Nephropathy is a common problem in diabetic patients, often leading to the need for haemodialysis or kidney transplant. XL784 has been optimised to be matrix metalloprotease-1 (MMP-1) sparing, with the aim of enhancing its safety profile and enabling higher dosing compared with other metalloprotease inhibitors.

The Phase II results were presented during a poster session at the American Society of Nephrology Renal Week 2007 meeting in San Francisco in November. 125 subjects were enrolled into the randomised, double-blind, placebo-controlled study. XL784 (200mg once daily for 12 weeks) was compared with placebo in subjects with macro-albuminuria who were being treated concurrently with an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin receptor blocker (ARB).

The primary endpoint was the reduction from baseline in the urinary albumin to creatinine ratio (ACR) at week 12. Albumin excretion is a risk factor for kidney failure, stroke and cardiovascular and all-cause mortality, particularly in patients with diabetes and/or hypertension. After 12 weeks, the baseline normalised ACR in the XL784 group was 9.9% lower than that in the placebo group (not significant). There was a clinically relevant mean ACR reduction from baseline of 23% (p=0.0027) in subjects randomised to XL784. The change in glomerular filtration rate at week 12 was -2.5 ml/min/1.73m2 in the XL784 group and -6.2 ml/min/1.73m2 in the placebo group (p=0.077).

The benefit of XL784 compared with placebo increased with increasing dose of ACEi and/or ARB. In the subgroup of subjects treated with maximum recommended doses of ACEi and/or ARB, the difference between XL784 and placebo was 23% (p=0.13) for the primary analysis population.

XL784 was generally well-tolerated, with fewer subjects reporting adverse events in the XL784 group (77%) than in the placebo group (85%). Serious adverse events (SAEs) were reported by 9.5% of subjects in the XL784 group and by 11% of subjects in the placebo group. No SAEs were considered to be related

to XL784. Article submitted by www.jobs4dd.com, a specialist online jobs board and news archive for the clinical trial and drug development sectors.

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