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MEETING ABSTRACT

A3.2

Safety, pharmacokinetics, pharmacodynamics and immunogenicity of a new anti-TNFα monoclonal antibody (GSK2800528)

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Background: GSK2800528 is an anti-TNFα monoclonal antibody. It has an identical amino acid sequence to adalimumab, the market leading anti-TNFα, except for three amino acid substitutions in the Fc portion of the molecule (YTE = M252Y/S254T/T256E) designed to increase antibody recycling, to reduce clearance and increase half-life. This is the first study of GSK2800528 in humans.

Methods: Fourty-five healthy volunteers, male or female between 18 and 65 years old, took part in a single-centre study (NCT01899755) conducted at Hammersmith Medicines Research. Subjects were split in to 4 cohorts: cohorts 1–3 received either a single dose of GSK2800528 (10, 40 or 160 mg) or placebo; cohort 4 received a single dose of adalimumab (40 mg). Safety and tolerability was closely monitored throughout, and blood samples were taken for assessment of drug concentration, anti-drug antibodies and pharmacodynamic markers (including an *ex vivo* whole-blood assay measuring IL-8 release in response to exogenous TNFα). A population PK analysis was performed on GSK2800528 and adalimumab PK data using NONMEM 7.1.2.

Results: There were no serious adverse events (SAEs), significant AEs, or AEs of special interest. There were no clinically significant changes in biochemical parameters, urinalysis parameters, vital signs, or ECG parameters in any treatment group. The PK of GSK2800528 was linear over the 10 to 160 mg range. A two-compartment model with first-order absorption and elimination was identified to describe both GSK2800528 and adalimumab data. The population-predicted apparent systemic clearance (CL/F) of GSK2800528 and adalimumab was 7.07 ml/h (10.3% RSE) and 18.4 ml/h (12.3% RSE) respectively, resulting in a mean fold reduction in CL/F of 2.6 (1.84–3.5). All subjects in the 40 mg GSK2800528 and 40 mg adalimumab cohorts showed inhibition of IL-8 release at day 7 post-dose. By day 56, IL-8 levels in the adalimumab cohort had returned to approximately baseline whereas IL-8 levels in the GSK2800528 cohort remained inhibited. All subjects dosed with GSK2800528 ($n = 27$) had detectable anti-drug antibodies by day 84. 23 of 27 (85%) subjects dosed with GSK2800528 had neutralizing anti-GSK2800528 antibodies. All subjects dosed with adalimumab ($n = 9$) had detectable anti-drug antibodies by day 140. Neutralizing antibodies were detected in 8 of the 9 (89%) subjects dosed with adalimumab.

Discussion: GSK2800528 was well tolerated and the PK profile showed the expected increase in half-life. Modelling suggested that GSK2800528 40 mg dosed every 4 weeks would provide similar exposure to adalimumab 40 mg dosed every 2 weeks. The *ex vivo* IL-8 assay demonstrated sustained levels of pharmacologically active drug on day 56 in the GSK2800528 cohort in contrast to the adalimumab cohort. The incidence and titer of anti-drug antibodies following a single dose of GSK2800528 or adalimumab were comparable.

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