Proceedings of the British Pharmacological Society at http://www.pA2online.org/abstracts/Vol11Issue3abst002P.pdf

A PK/PD Study Of A Selective A2a Agonist, (GW328267X) A Potential IV Therapeutic For Acute Lung Injury: No Tachyphylaxis To The Heart Rate Effect

A Allen[1], A Koch[4], N Garman[1], A Cahn[1], OE Dewitt[3], CN Rambaran[2]. [1]GlaxoSmithKline R&D, Stevenage, Hertfordshire, UK, [2]GlaxoSmithKline R&D, Stockley Park, Uxbridge, Middlesex, UK, [3]GlaxoSmithKline R&D, Cambridge, Cambs, UK, [4]Parexel International, Northwick Park Hospital, Harrow, Middlesex, UK

GW328267X is a potent and selective agonist at the human adenosine A_{2a} receptor and antagonist at the human adenosine A_3 receptor that was previously in development as an inhaled formulation for asthma. Based on preclinical data in rodents A2a agonists are potent anti-inflammatories and recent evidence in models of acute lung injury (ALI) indicated that GW328267X had the potential to be developed as an intravenous (IV) formulation for the treatment and prevention of ALI. An issue previously identified with this mechanism after dosing in healthy volunteers and patients is that activity on A2a receptors in the carotid bodies results in an exposure related tachycardia resulting in an unacceptable tolerability profile. The potential for the development of tachyphylaxis to this undesired effect has never been investigated but if present would allow the potential for use of an A2 agonist as an IV infusion delivered in a dose escalating manner in clinical environments with continuous heart rate (HR) monitoring such as the intensive care unit (ITU). In this setting an effect on platelet aggregation and erythropoietin levels which have been previously demonstrated in preclinical studies with A2a agonists, would also be beneficial.

This was a single centre, open label, dose escalating, two cohort study [A2L115387, NCT01640990] in healthy male volunteers, intended to evaluate the tolerability, safety, pharmacokinetics and pharmacodynamics of GW328267X after slow IV infusion of doses of 8mcg/h for 1.5 hrs followed by 10mcg/h for 4 hrs. A total of 3 subjects were initially enrolled in the study and there was a sequential increase in HR starting from approximately 1 hour after the start of the IV infusion with all 3 subjects meeting predefined stopping criteria. The infusion was stopped as follows: in Subject 1 after 3.75 hrs and an increase in HR from baseline of 30bpm for 10 mins; in Subject 2 after 3.82 hrs and an increase in HR from baseline of 40 bpm for 2 mins; in Subject 3 after 2.65 hrs and intolerable nausea. There was no significant effect on either systolic or diastolic blood pressure during the infusion. Drug systemic exposures were in line with those predicted and there was no significant inhibition of platelet aggregation and no effect on serum erythropoietin levels during and up to 24 hours after initiation of the IV infusion.

GW328267X given as an escalating slow IV infusion was poorly tolerated, with no evidence of tachyphylaxis to the HR effect observed during the infusion at the doses used. The study was therefore not progressed further.

Study A2L115387 was funded by GlaxoSmithKline® (GSK®).