

AstraZeneca	AZD4017
<b>Mechanism of Action</b>	11-beta-hydroxysteroid dehydrogenase type 1 (11 $\beta$ -HSD1) inhibitor <a href="http://www.ncbi.nlm.nih.gov/gene/3290">http://www.ncbi.nlm.nih.gov/gene/3290</a>
<b>Overview</b>	AZD4017 is a competitive, fully reversible inhibitor of human recombinant 11 $\beta$ -HSD1 (IC <sub>50</sub> of 2 nM) and of 11 $\beta$ -HSD1 activity in isolated human adipocytes (1.8 nM) with cortisone as substrate. It is selective (>2000x) over human recombinant 11 $\beta$ -HSD2 and other closely homologous enzymes <i>in vitro</i> . AZD4017 has limited activity in pre-clinical tests in species other than cynomolgus monkey. However, related tool compounds with activity in all species are available; e.g., in diet-induced obese mice, a rodent-active AstraZeneca 11 $\beta$ -HSD1 inhibitor induced significant, and approximately half-maximal, reduction in adipose mass and weight gain when compound exposure was near the IC <sub>50</sub> .
<b>Safety/Tolerability</b>	<p>In single ascending dose studies, Caucasian and Japanese volunteers were exposed to AZD4017 dosed up to 750 mg twice daily (BID). In a multiple ascending dose (MAD) study, volunteers received single doses of AZD4017 followed by repeated doses ranging from 75 mg every day (QD) up to 900 mg BID for 9 days. A few subjects on treatment had transient increased liver enzyme levels above the upper limit of normal (ULN; &gt;3x ULN in one subject) with no concurrent increase in bilirubin. An activation of the hypothalamic-pituitary-adrenal (HPA) axis was demonstrated by an increase in ACTH and DHEA levels and by an increase of total urinary glucocorticoid metabolites. However, s-cortisol and testosterone levels were not changed. In a Phase 2a glaucoma study, a number of subjects had incidences of elevated liver enzymes near the ULN, but with no associated adverse events.</p> <p>Preclinical toxicity studies of up to 3-month duration have been performed in rat and non-human primate. Changes in adrenal glands were noted in both preclinical species but were considered an adaptive response of this organ to altered function. Findings in the liver and the thyroid gland of rat were also considered adaptive and not degenerative in nature.</p>
<b>Additional Information</b>	In a 9-day proof of mechanism (PoM) study, AZD4017 (1200 mg QD) significantly inhibited hepatic 11 $\beta$ -HSD1 activity as measured by an oral prednisone challenge. Measurements of urine glucocorticoid metabolites further indicate an inhibitory effect on the whole-body 11 $\beta$ -HSD1 activity. Regarding the 11 $\beta$ -HSD1 inhibitory effect in adipose tissue, a MAD and PoM study in abdominally obese subjects demonstrated inhibition of 11 $\beta$ -HSD1 after single dosing, yet no sustained inhibitory effect after repeated doses at the tested dose levels. However, <i>ex vivo</i> investigations suggest the possibility of obtaining inhibition after repeated dosing at high AZD4017 concentrations. In a 28-day Phase 2a study in patients with raised intraocular pressure (IOP), AZD4017 dosed at 400 mg BID produced no change in IOP when compared to placebo (plasma concentrations of about 10 times the IC <sub>50</sub> ).
<b>Suitable for and Exclusions</b>	Preclinical reproductive toxicology data are not available for this compound. The inclusion of women of child-bearing potential using highly effective contraception in trials of modest size and duration could be considered based on the risk-benefit and in accordance with territory-specific requirements. Preclinical safety studies support future clinical studies of up to 3-month duration with the need for monitoring liver enzymes, thyroid and adrenal function.
<b>Clinical Trials</b>	<a href="http://www.clinicaltrials.gov/ct2/results?term=AZD4017&amp;Search=Search">http://www.clinicaltrials.gov/ct2/results?term=AZD4017&amp;Search=Search</a>
<b>Additional Characteristics: CNS Penetration/Pediatric Diseases</b>	AZD4017 has low CNS penetration and, thus, is probably not suitable for a CNS indication.  Pediatric disease projects cannot be supported at this time.
<b>Publications</b>	<a href="http://www.ncbi.nlm.nih.gov/pubmed/?term=AZD4017">http://www.ncbi.nlm.nih.gov/pubmed/?term=AZD4017</a>