Pfizer Inc.	CE-326597
Mechanism of Action	Cholecystokinin 1 receptor (CCK-1R) (or CCK_A receptor) agonist http://iuphar-db.org/DATABASE/ObjectDisplayForward?objectId=76 http://www.ncbi.nlm.nih.gov/gene/886
Overview	CE-326597 is a potent (Ki = 36 nM), selective (over a broad range of transporters, uptake sites, ion channels and receptors) agonist of the human and rat CCK-1R. Cholecystokinin is a regulatory peptide hormone with action at two distinct receptors, CCK-1 and CCK-2. CCK-1Rs are located predominantly in the gastrointestinal tract where they are responsible for several functions including satiety (via vagal afferents), delayed gastric emptying, and motility of the gallbladder.
Safety/Tolerability	CE-326597 at 5 – 100 mg QD for 12 weeks appeared to be well-tolerated in overweight subjects with Type 2 Diabetes Mellitus (T2DM). Mild to moderate, self-limited GI symptoms were observed with increasing dose. Nonclinical toxicology data support clinical studies up to 3 months in duration.
Additional Information	CE-326597 produced modest reductions in both Hemoglobin A1c (HbA1c) and body weight at the 50 mg QD dose for 12 wks in overweight T2DM subjects. The magnitude of effect, however, was insufficient, did not meet pre-defined criteria, to advance further. Gallbladder contraction (as assessed by transabdominal ultrasonography) was observed with both single and multiple doses of CE-326597. A midazolam drug-drug interaction study suggested that CE-326597 is not a sizeable inhibitor of CYP3A4.
Suitable for and Exclusions	Given that CE-326597 (at ≥ 10 mg) causes gallbladder contraction and there is a theoretical risk of biliary obstruction with expulsion of cholelithiasis, enrollment in initial Phase 1b/2a trials should be limited to subjects without cholecystolithiasis/cholelithiasis. Since *in vitro* data indicates that CE-326597 inhibits P-glycoprotein (P-gp), agents known to be P-gp substrates with narrow therapeutic margins should be avoided in, at least initial, clinical studies.
Clinical Trials	http://www.clinicaltrials.gov/ct2/results?term=CE-326%2C597
Publications	http://www.ncbi.nlm.nih.gov/pubmed/22157397