

### 3. CLINICAL PHARMACOLOGY

- The clinical pharmacology program established the pharmacokinetic and, pharmacodynamic profiles of cilomilast in 1297 human subjects enrolled into 51 studies.
- Cilomilast demonstrated complete oral absorption and negligible first-pass metabolism. It has very high plasma protein binding (99.4%), but with a large binding reserve. The steady-state volume of distribution (typically 10 – 17L) is small.
- Cilomilast exhibited slow metabolic clearance through multiple, parallel pathways to metabolites with lower potency (at least 10-fold) which were rapidly cleared in the urine.
- The elimination half-life was seven hours. The pharmacokinetics of cilomilast were dose- and time-independent and showed low variability. Steady-state plasma concentrations were achieved within two days of BID dosing.
- With the exception of dose limiting nausea and vomiting, the safety and tolerability profile of cilomilast were similar to placebo. The highest dose tolerated by patients was 15mg BID.
- Pharmacodynamic studies designed to follow-up non-clinical safety findings did not demonstrate evidence of gastrointestinal, cardiovascular, male reproductive or neuroendocrine system safety issues in humans.
- Investigations involving the elderly, smokers, Japanese and Chinese subjects did not exhibit pharmacokinetic, pharmacodynamic or tolerability differences, therefore no dose adjustment is required.
- Studies in patients with hepatic and renal impairment demonstrated an increased exposure to unbound cilomilast and the potential for reduced gastrointestinal tolerability.
- In patients with COPD, pharmacokinetic parameter estimates were consistent with those in healthy subjects - therefore routine monitoring of plasma concentrations while treating patients with COPD is not indicated.
- Cilomilast had no pharmacokinetic or pharmacodynamic interactions with a range of drugs likely to be co-administered in patients with COPD with the exception of erythromycin which was not well tolerated. Metabolism based drug-drug interactions are not anticipated.

#### 3.1. Program objectives and overview

The primary objectives of the clinical pharmacology program were the characterization of the safety, tolerability and pharmacokinetic profiles of oral cilomilast in humans. These investigations included a range of doses and also assessed the influence of environmental, demographic and relevant pathophysiological factors. Relationships

between dose or exposure and pharmacodynamic effects were studied. The potential for interactions with medications likely to be co-administered with cilomilast was examined.

There were fifty-one clinical studies and one meta-analysis in the clinical pharmacology program. Of the 931 subjects enrolled into the studies, 829 (676 male and 153 female) were healthy and 102 (62 male and 40 female) had pulmonary, renal or hepatic disease. Thirty-four of the healthy subjects were aged 65 years or older. The population pharmacokinetics of cilomilast were also characterized in over 1,000 patients with COPD in three clinical efficacy studies.

### **3.2. Pharmacokinetic characteristics**

#### **3.2.1. Absorption and Bioavailability**

- Cilomilast demonstrates complete oral absorption and negligible first-pass metabolism. Although this was unaffected by food, it is recommended that cilomilast is taken with food, because gastrointestinal tolerability may be improved.

The oral bioavailability (F) of cilomilast in the fasted state was approximately 100%. Absorption was rapid with drug appearing in the plasma within 15 minutes of dosing and maximum plasma concentration (C<sub>max</sub>) occurring within 2 hours. A high fat breakfast did not affect the extent of absorption (AUC), but delayed time to maximum concentration (T<sub>max</sub>) by 2 hours and reduced C<sub>max</sub> by 39%. Since AUC is unaffected, cilomilast can be administered without regard to dietary state. However, it is recommended that it be taken with food because gastrointestinal tolerability may be improved.

#### **3.2.2. Distribution**

- Cilomilast was very highly bound to plasma proteins and has a small steady-state volume of distribution.

Plasma protein binding of cilomilast was 99.4%, but not saturable at concentrations 30 times greater than C<sub>max</sub> at the therapeutic dose. Given this significant binding reserve, displacement interactions are considered unlikely. Binding occurred preferentially to albumin and was reversible. The steady-state volume of distribution (V<sub>ss</sub>) after intravenous administration was typically 10 to 17 L.

#### **3.2.3. Metabolism and Elimination**

- Cilomilast exhibits slow plasma clearance (typically 1.5 – 2 L/h) through multiple metabolic pathways. The metabolites are rapidly eliminated in urine and do not contribute to its clinical profile.
- The elimination half-life was 7 hours.

Unchanged cilomilast accounted for at least 70% of the total systemic exposure in plasma and less than 1% of the dose excreted in urine. Three major, parallel metabolic pathways

were identified - hydroxylation, decyclopentylation and acyl glucuronidation. Metabolites were eliminated rapidly and mostly in the urine (>90% of dose).

The hydroxylation pathway, forming the most abundant metabolite (SB-217493) was catalysed by the hepatic cytochrome P450 (CYP) 2C8. CYP2C8 has few known inhibitors and inducers of CYP2C8 are considered unlikely to influence its clearance. At therapeutic concentrations, cilomilast is not expected to inhibit or induce a wide range of cytochromatic enzymes, including CYP2C8. Metabolic drug-drug interactions are not anticipated.

While unbound plasma concentrations of cilomilast and its 3-hydroxy metabolite are similar the pharmacological activity of this metabolite is 10 to 15-fold less than that of cilomilast. It is, therefore, unlikely to contribute significantly to the therapeutic profile.

### 3.2.4. Dose linearity

- Cilomilast exhibited dose and time independent pharmacokinetics with low variability. Steady-state plasma concentrations are achieved within two days of BID dosing.

Cilomilast pharmacokinetics were dose-proportional and between-subject variability was low (CV <30% for C<sub>max</sub> and AUC) following both single (2 and 20 mg) and repeat (2 to 30mg BID) oral administration, with half-life and T<sub>max</sub> remaining constant. Cilomilast clearance, volume of distribution at steady state, and plasma half-life also remained constant across the intravenous dose range of 1 to 4mg.

Cilomilast steady-state was reached within 2 days of BID dosing. Steady-state pharmacokinetics were predicted by single dose data.

### 3.3. Safety and tolerability

- With the exception of headache, nausea and vomiting, the overall safety and tolerability profile of cilomilast at a dose of 15mg BID was similar to that of placebo.

The five most common on-therapy adverse events in subjects receiving oral cilomilast or placebo are listed below (subject sessions with one or more events as percentage of total subject sessions):

Adverse event	Placebo	Cilomilast
Headache	20.0 %	31.6 %
Nausea	5.7 %	14.8 %
Dizziness	4.3 %	5.6 %
Vomiting	2.4 %	5.0 %
Diarrhea	5.7 %	4.2 %

There was evidence that cilomilast was better tolerated, with respect to gastrointestinal adverse events, when administered with food.

### **3.3.1. Maximum tolerated dose**

- Single doses of 20mg resulted in an increase in nausea and vomiting, identifying 15mg as the maximum tolerated single dose.

Proposed repeat dosing with cilomilast 20mg BID in fasted individuals was terminated after first dosing because of nausea and vomiting. Therefore, to ensure acceptable tolerability, only doses up to 15mg BID were selected for evaluation in the patient dose-ranging studies and trials of therapeutic effectiveness and safety.

## **3.4. Pharmacokinetics, safety and tolerability in special populations**

### **3.4.1. Elderly and smokers**

- Elderly subjects and smokers did not exhibit pharmacokinetic or tolerability differences; therefore no dose adjustment is required.

### **3.4.2. Japanese and Chinese subjects**

- Japanese and Chinese subjects do not require dose adjustment.

Although systemic exposure and maximal plasma concentrations of cilomilast were generally higher (20 to 30%) in Japanese and Chinese subjects compared with those seen in Caucasians following single and repeat doses, disposition was in all other respects similar. Lower average body weight in these ethnic groups may account for this. The safety and tolerability profile of cilomilast appeared to be similar to that seen in Caucasians.

### **3.4.3. Hepatic and renal impairment**

- Studies in patients with hepatic and renal impairment demonstrated an increased exposure to unbound cilomilast and the potential for reduced gastrointestinal tolerability.

In subjects with renal impairment, as creatinine clearance (CL<sub>cr</sub>) decreased, cilomilast unbound steady state AUC was elevated and the elimination half-life was prolonged. Compared with a typical healthy subject (CL<sub>cr</sub> 120mL/min), predicted average increases in unbound AUC were 29%, 43%, 65%, and 79% in patients with CL<sub>cr</sub> values of 80, 60, 30, and 10 mL/min, respectively. Predicted average half-lives at these CL<sub>cr</sub> values were 8.5, 9.6, 11.2, and 12.3 hours, respectively. In subjects with renal impairment, increased exposure to unbound cilomilast appeared to be associated with an increase in the incidence of nausea and vomiting adverse events.

In hepatic impairment, unbound exposure was found to be greatest in the most severely impaired group. Compared to healthy subjects, cilomilast unbound AUC after a single 10mg dose was elevated approximately 2-fold in subjects with moderate hepatic impairment (Child-Pugh Grade B, n = 6) and approximately 5-fold in severe hepatic impairment (Child-Pugh Grade C, n = 4). There were no significant differences in cilomilast elimination half-life between the groups. In this study, there was no increase in GI adverse events in patients with moderate and severe hepatic impairment, however an increase in unbound cilomilast may be associated with an increased in GI adverse events. There are no data in subjects with mild hepatic impairment, at the clinical dose of 15mg BID, or with repeat dosing.

### **3.5. Population pharmacokinetics in patient with COPD**

- Pharmacokinetic parameter estimates were consistent with those in healthy subjects.
- Routine monitoring of plasma concentrations is not warranted.

A one-compartment model with first order absorption and elimination adequately described the pharmacokinetics of cilomilast in patients with COPD receiving 15 mg BID for 24 weeks. Parameter estimates in patients with COPD were consistent with those in healthy subjects.

Body weight was the only demographic factor which significantly influenced cilomilast disposition. Clearance (CL/F) and volume of distribution at steady-state ( $V_{ss}/F$ ) uncorrected for bioavailability increased by approximately 0.08 L/h and 1 L, respectively, for each 10kg increase in body weight. These changes are small at body weights in the range 50 to 100kg, the resulting spread in steady state AUC values was less than  $\pm 20\%$ . Dose adjustments based on body weight are therefore not warranted.

Neither age, gender, creatinine clearance nor smoking were found to significantly affect CL/F or  $V_{ss}/F$ . No correlation between cilomilast systemic exposure and COPD efficacy was evident. Similarly, no clinically relevant relationships were demonstrated between plasma concentrations and gastrointestinal adverse events during chronic administration.

### **3.6. Pharmacokinetic and pharmacodynamic interactions with other drugs**

- Cilomilast had no pharmacokinetic or pharmacodynamic interactions with a range of drugs likely to be co-administered in patients with COPD with the exception of erythromycin which was not well tolerated.
- No metabolism based drug-drug interactions would be anticipated with drugs cleared by cytochrome P450 isoenzymes (see Section 3.2.3).

No significant pharmacokinetic or pharmacodynamic interactions were observed and the tolerability of cilomilast was not affected by co-administration with albuterol, ipratropium, theophylline, prednisolone, warfarin and digoxin.

Co-administration of cilomilast and erythromycin resulted in an increase in gastrointestinal adverse events without any significant change in the pharmacokinetic

profile of either drug. However, this effect was reduced if cilomilast was brought to steady-state prior to initiation of the erythromycin.

Cilomilast bioavailability was not affected by co-administration with a magnesium-aluminium-dimethicone antacid, but absorption was blocked almost completely by activated charcoal, which may therefore have a role in treatment of over-dose.

### **3.7. Pharmacodynamic effects relevant to safety and tolerability**

- Pharmacodynamic studies designed to follow-up non-clinical safety findings did not demonstrate evidence of gastrointestinal, cardiovascular, male reproductive or neuroendocrine system safety issues in humans.

#### **3.7.1. Gastrointestinal system**

In non-clinical studies, vomiting was observed in non-rodent species and was attributed to the pharmacological action of cilomilast. This effect was also evident in the clinical pharmacology studies.

Investigation in healthy subjects showed that 15mg BID cilomilast had only minor activity on lower esophageal sphincter pressure and gastrointestinal transit time. There were no significant effects on gastric pH. It was concluded that no clinically important effects had been observed.

#### **3.7.2. Cardiovascular system**

Medial arterial necrosis was observed in rats and was considered likely to be secondary to haemodynamic changes resulting from the vasodilatory effects of cilomilast in the rat. No adverse effects arising in the clinical pharmacology program could be attributed to arterial pathology, and in particular to the splanchnic arteries.

Focal myocardial necrosis was seen in rats at  $\geq 80\text{mg/kg/day}$  and was considered to be an agonal event secondary to multiple organ failure. Evidence for cardiovascular changes in humans was investigated by collecting 12-lead ECG data, Holter monitoring, semi-supine, supine and erect pulse rate and systolic and diastolic blood pressure. Seventeen clinical pharmacology studies provided specific cardiovascular safety and tolerability data. A meta-analysis was performed on data from nine of the studies.

Overall, there was no evidence of clinically important changes in blood pressure, heart rate or ECG waveform or specific interval measurements, including QTc. There was no evidence that the incidence of arrhythmias, as assessed by Holter monitoring, was greater with cilomilast compared to placebo.

#### **3.7.3. Male reproductive system**

Testicular degeneration was observed in rats and rabbits. In rats this finding was considered likely to be secondary to hemodynamic changes resulting from the vasodilatory effects of cilomilast ( $\geq 80\text{mg/kg/day}$  for one month). In rabbits this finding

was considered most likely to be an exacerbation of a spontaneous background finding, although a relationship to treatment could not be discounted (3 - 60mg/kg/day for 1 month).

In order to investigate effects in the human reproductive system, cilomilast was administered at a dose of 15mg BID to 64 healthy, young male subjects for 12 weeks. There was a parallel placebo group of 36 subjects. The subjects were followed for 12 weeks from the end of dosing (57 cilomilast and 31 placebo group subjects completed the study). Analysis of the primary endpoints (total number of sperm per ejaculate, progressive and overall motility and morphology) did not demonstrate any statistically significant differences for cilomilast compared to placebo, except for an increase in sperm motility in the cilomilast group at one time point (day 85).

A secondary endpoint, mean sperm concentration, showed a statistically significant decrease for cilomilast as compared to placebo, at the final follow-up assessment (day 169). In the cilomilast treatment group, there was no change from baseline in sperm concentration while there was an increase in the placebo treatment group. These findings were not considered to be of clinical importance.

#### **3.7.4. Neuroendocrine system**

Adrenocortical hypertrophy was observed in rats and is a well-recognized response of rats to PDE4 inhibitors. This is due to stimulation of ACTH release in response to increased cAMP concentrations in the hypothalamus and anterior pituitary gland.

In a 2 year, oral carcinogenicity study in mice, a weak effect for mammary tumor induction was observed at 100mg/kg/day. This was associated with microscopic changes consistent with hyperprolactinemia. There was no evidence for changes in prolactin levels, but persistent diestrus was observed. The mammary gland lesions were therefore considered likely to be related to cilomilast induced pseudopregnancy. No such findings were observed in rats and there is no human analogy of pseudopregnancy. It was therefore considered that these tumors were unlikely to be of clinical relevance.

A clinical pharmacology study was conducted in humans to explore the effects of cilomilast on the HPA axis and prolactin secretion. Serum ACTH, cortisol and prolactin and urinary cortisol levels were not significantly different following repeat dosing of cilomilast and placebo. Additional assessments of HPA axis function were made in six other clinical pharmacology studies and demonstrated similar findings. The results indicated that levels of prolactin, ACTH, serum cortisol and urinary cortisol were similar following repeat dosing with cilomilast and placebo.