Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Iloperidone

Proprietary Product Name: Fanapt

Sponsor: Kendle R&D Pty Limited

June 2012

TGA Health Safety Regulation

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I. Introduction to Product Submission

Submission Details

Type of Submission	New Chemical Entity
Decision:	Rejected
Date of Decision:	20 December 2011
Active ingredient(s):	Iloperidone
Product Name(s):	Fanapt
Sponsor's Name and Address:	Kendle R&D Pty Limited
	20 Atherton Road, Oakleigh, VIC 3166
Dose form(s):	Tablets
Strength(s):	1, 2, 4, 6, 8, 10 & 12 mg
Container(s):	Blister packs
Pack size(s):	Commercial packs: 28 tablets (all strengths)
	Physician sample packs: 14 tablets (all strengths)
	Titration pack: two each of the 1, 2, 4 & 6 mg tablets
Approved Therapeutic use:	Not applicable
Route(s) of administration:	Oral
Dosage:	1 mg twice daily, increasing to the target dose range of 6-12 mg twice daily via daily dose increments of 2 mg twice daily over up to 7 days.
ARTG Number (s)	Not applicable

Product Background

Iloperidone (ILO) is an atypical antipsychotic, belonging to the chemical class of piperidinyl-benzisoxazole derivatives. *In vitro* receptor profiling, nonclinical pharmacology and second messenger studies have shown ILO antagonises and has high affinity for dopaminergic, serotonergic and adrenergic (including the subtypes 5HT2A/5-HT1A/D2/D3/NEa1/NEa2C) receptors in humans.

This AusPAR describes the application made by the sponsor to register the new chemical entity, ILO (as Fanapt), for the following indication:

> *Fanapt is indicated for the treatment of psychotic symptoms in patients with schizophrenia.*

The proposed indication specifies treatment of psychotic symptoms rather than for schizophrenia. This is a significant departure from the usual indications for more recently registered antipsychotic medicines as these specify a clinical condition rather than a symptom occurring in patients who have a clinical condition (in this case, schizophrenia). This is the approach recommended in the TGA adopted European Union (EU) guideline

Note for Guidance on the Clinical Investigation of Medicinal Products in the Treatment of Schizophrenia.[1]

The dose range for which approval is sought is 12 – 24 mg a day.

Clinically relevant high rates of significant adverse events have been reported with all the antipsychotic medications. As a class, the atypicals have been associated with akathisia, extrapyramidal side effects, weight gain, sedation, metabolic changes, and the sequelae of hyperprolactinemia.

Regulatory Status

The following table (Table 1) summarises the international regulatory status of Fanapt.

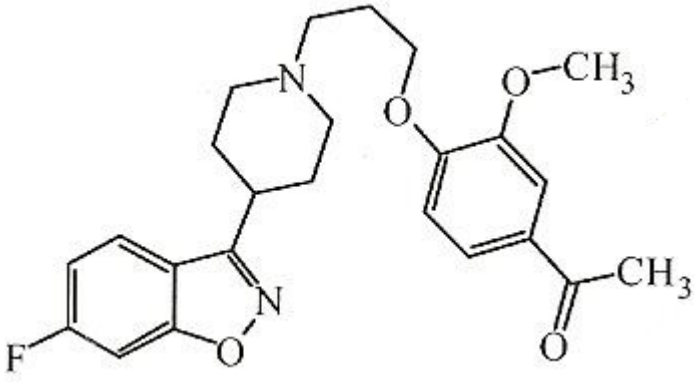
Fanapt was approved by the FDA in May of 2009 '*for the treatment of schizophrenia in adults'*. A similar application has also been lodged in the European Union (centralised procedure) where a decision was pending at the time of this AusPAR.

II. Quality Findings

Drug Substance (active ingredient)

ILO is a synthetic drug substance with the following structure.

Figure 1. Chemical structure of Iloperidon.



It contains no chiral centres and is obtained as a crystalline powder with no known polymorphs. It has a basic pKa of 7.69. It is practically insoluble in water but more soluble at lower pH. It has an octanol/water partition coefficient at pH 7.0 of 374 (log P 2.57) and is highly permeable in Caco-2 cell experiments. It is classified under the Biopharmaceutics Classification System as BCS Class 2[2].

The drug substance is milled to meet the particle size specification. There are three impurities with limits that exceed the International Conference on Harmonisation (ICH) qualification threshold but the Medicines Toxicology Evaluation Section at the TGA has advised that those limits have been satisfactorily qualified.

[1] CPMP/EWP/559/95. http://www.tga.gov.au/pdf/euguide/ewp055995en.pdf

[2] The Biopharmaceutics Classification System (BCS) is a guidance for predicting the intestinal drug absorption provided by the U.S. Food and Drug Administration. According to the BCS, drug substances are classified as follows: Class I: high permeability, high solubility; Class II: high permeability, low solubility; Class III: low permeability, high solubility; Class IV: low permeability, low solubility.

Drug Product

The tablets are uncoated and unscored tablets, manufactured by a conventional wet granulation process. Although the same excipients are used in all strengths, four slightly different granulation formulations are used to manufacture the seven strengths of tablet proposed for registration.

The assay limits applied to the tablets have been tightened as requested by the evaluator following the initial evaluation of this submission. Limits for degradants are within the ICH qualification threshold.

The method used to test the dissolution limit has been shown to be discriminatory.

Originally, the sponsor proposed packaging the tablets in high density polyethylene (HDPE) bottles but the packaging was changed to blister packs at the request of the TGA because of the greater potential for intentional overdose if the tablets are presented in bottles. Adequate stability data have been provided in blister packs to support a shelf life of 3 years below 25°C.

Biopharmaceutics

Nine bioavailability studies were submitted. Six of these studies described in the following table (Table 2) were considered to be not directly relevant to formulation aspects and were not evaluated by the quality evaluator.

Table 2. Bioavailability studies not evaluated.

Study Number*	Comments
101, 103 & 106	Bioavailability studies on early formulations.
104	Pharmacokinetic study in extensive and poor cytochrome P450 (CYP) subtype 2D6 metabolisers.
112	Steady state dose proportionality study; titration with 1 mg tablet followed by pharmacokinetic assessment at doses of 2, 4, 8 & 12 mg bid. These doses all used the 4 mg tablet (halved when necessary).
1001	Study on a controlled release tablet that is not part of the present application.

* abbreviated to the terminal numeric part of the study number. bid=twice a day.

Study 105 showed that the 1 mg tablet proposed for registration has a 14% lower ILO peak plasma concentration (C_{max}) than an oral solution of the drug in 2.5% propylene glycol/acetate buffer but is bioequivalent in terms of the ILO area under the plasma concentration time curve (AUC). The tablet and oral solution were fully bioequivalent with regard to the major, active metabolite, P88.

Study 105 also showed that food has no significant effect on the bioavailability of the 1 mg tablet, with regard to both ILO and P88.

Study 110 compared, under fasting conditions, the three formulations that have been used in clinical studies: an over-encapsulated clinical trial tablet, the over-encapsulated tablet proposed for registration and the 'naked' tablet proposed for registration. The three formulations were shown to be bioequivalent.

Study 1002 compared the over-encapsulated tablet proposed for registration with the 'naked' tablet proposed for registration under fed conditions. The two formulations were found to be bioequivalent with regard to both ILO and P88 except that the over-encapsulated tablet had a 14% higher ILO C_{max} than the naked tablet.

A number of deficiencies in these three bioavailability studies were identified by the evaluator during the initial evaluation of this submission. The sponsor subsequently

addressed some of those deficiencies (such as the inappropriate calculation of terminal half lives) by re-analysing the study results. The sponsor also provided stability data for ILO and its metabolites in plasma and evidence for the absence of matrix effects in the analytical method. The supplementary information and analyses provided were adequate to confirm the study results summarised above.

Quality Summary and Conclusions

This submission was considered by the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM) at its 139th meeting on 25 July 2011. The PSC endorsed the issues that had been raised by the TGA and these issues have now been satisfactorily resolved. The PSC requested analytical data for three consecutive, full scale batches of the drug substance, which have since been provided to the TGA. The PSC agreed that the sponsor's justifications for not conducting an absolute bioavailability study and for not conducting bioequivalence studies on all strengths of Fanapt tablets were acceptable.

There were no further outstanding issues and there were therefore no objections in respect of Chemistry, Manufacturing and Controls to registration of Fanapt tablets.

III. Nonclinical Findings

Introduction

The current nonclinical submission was considered sufficient, although there were some shortcomings, many of which probably related to the history of this drug, and the sponsor's nonclinical overview was particularly superficial. Many studies were dated (1990-1995), and those relating to safety pharmacology were not comprehensive and generally not Good Laboratory Practice (GLP)-compliant. Toxicokinetic data were not always available.

Pharmacology

In vitro receptor binding data were compiled from studies from several laboratories conducted over a number of years under different experimental conditions and were quite variable. Overall, however, they revealed high affinity of ILO for human and rat dopamine, α-adrenergic and serotonin (5-HT) receptors. ILO also showed high affinity for sigma receptors (guinea pig). For human receptors, ILO generally showed moderate-high affinities for all dopamine receptor subtypes (D_1, D_2, D_3, D_4 and D_5), while for 5-HT receptors and α receptors, the highest affinities were for the 5-HT_{2A} and the α_{1D} and α_{2C}.

Other characteristics of ILO binding were generally moderate affinity for human α_{2A}, α_{2B}, 5-HT_{1A}, 5-HT_{2C}, 5-HT_6 and 5-HT_7 and calf 5-$HT_{1B/1D}$ receptors, no affinity for human 5-HT_3 and high affinity for rat α_1 receptors. The antipsychotic activity of ILO is believed to be mainly attributable to its binding to D_2 and 5-HT_{2A} receptors. Concurrent comparisons of ILO binding characteristics with those of other antipsychotic drugs were limited. However, in one study risperidone (considered an atypical antipsychotic drug) and ILO showed similar affinities for both D_2 and D_3 receptors, while ILO showed greater affinity for D_1 receptors and risperidone showed greater affinity for D_4 receptors. In further *in vitro* functional studies with transfected cells expressing human dopamine (D_2 and D_3), serotoninergic (5-HT_{1A} and 5-HT_6) or α-adrenergic (α_{2A} and α_{2C}) receptors coupled to adenylate cyclase, ILO inhibited agonist responses in a concentration-dependent manner but had no agonist activity itself.

Results from a number of *in vivo* studies were consistent with the antagonistic activity of ILO at 5-HT and dopamine receptors, including inhibition of 5-HT induced head twitches

and antagonism of MK-801 (dizocilpine)-induced locomotion and falling behaviour and apomorphine-induced climbing behaviour. Further, ILO increased dihydroxyphenylalanine (DOPA) concentrations in rat striatum and nucleus accumbens, indicative of an increase in the turnover of dopamine which is consistent with its dopamine receptor antagonist properties. Levels of messenger ribonucleic acid (mRNA) for the D_2 receptor were increased in rat hippocampus and striatum after administration of ILO , consistent with central dopamine D_2 receptor blockade. ILO also showed some dopamine autoreceptor antagonist activity.

ILO was active in various *in vivo* models thought to be predictive of neuroleptic and anxiolytic activities, and like clozapine, increased social interaction in pairs of rats unfamiliar with each other, suggesting that it may have an ameliorative effect on the negative schizophrenic symptom of social withdrawal. However, in contrast to clozapine, ILO did not reverse phencyclidine-induced social deficits.

Many of the *in vivo* studies included clozapine and haloperidol as comparators, and as may be expected, in those relating to antagonism at dopamine receptors, all three agents showed similar activity. By contrast, in studies relating to antagonism at 5-HT_2 receptors, ILO and clozapine showed similar activity, while haloperidol showed little or no activity. These results are consistent with the receptor binding profile of ILO as an atypical antipsychotic agent. In studies relating to other activities, ILO showed activity more closely resembling that of clozapine in some studies and haloperidol in other studies, depending on the parameter that was investigated.

Metabolites

Major circulating metabolites in humans were P95 and the carbonyl reduction product P88, with the latter having *in vitro* receptor binding affinities that were generally similar to or slightly lower than those for ILO (human and/or rat dopamine, 5-HT and α-adrenergic receptors were investigated). By contrast, receptor binding of metabolite P95 differed from that of ILO , with high affinity binding only for α-adrenergic and 5-HT_{2A} receptors and lower affinity than ILO for dopamine and 5-HT (other than 5-HT_{2A}) receptors.

Overall, the pharmacodynamic results suggested that ILO would be efficacious for the proposed indication, although the extent to which it compared with other currently registered drugs will only be determined from the clinical studies.

Safety pharmacology

Results of *in vitro* tests (hERG current block and Purkinje fibre action potential prolongation) were suggestive of potential cardiac effects, although the main human metabolite P95 showed little or no activity. Hypotension and tachycardia were observed in dogs after oral (PO; capsule) treatment, but electrocardiogram (ECG) values (including QT intervals[3]) were unaffected, although it was difficult to determine likely C_{max} values with the doses used (5 and 15 mg/kg). Based on results of appropriate pharmacokinetic and toxicokinetic studies, these may have been either slightly or substantially higher than in humans, with this uncertainty reflecting non-linear kinetics and considerable inter-animal variation which characterised plasma measurements in dogs. Quantitative ECG examinations were conducted in the 13 and 52 week dog toxicity studies using high-doses of 24 or 25 mg/kg/day, but measurement times were respectively not stated or were prior to dosing. By contrast, QT interval prolongation has been observed in the clinical studies

[3] QT interval: a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias and sudden death.

(Sponsor's *Clinical overview*) and this is mentioned in the proposed Product Information together with orthostatic hypotension and tachycardia. Several non-GLP rat and dog cardiovascular studies of uncertain origin (but probably Hoechst studies) were also included, with salient PO findings of reduced blood pressure (both species) associated with lower total peripheral resistance (dogs). Anti-α_1 adrenergic activity was shown in rats (inhibition of phenylephrine pressor response), which is consistent with the strong affinity of ILO and its P88 and P95 metabolites for this receptor and probably explains these results.

The only other GLP-compliant *in vivo* safety pharmacology study failed to show any respiratory effects of ILO or metabolite P95. However, although the latter would have achieved a high C_{max} value relative to the expected human value (58 ng/mL, section 6.2.5), based on results from a pharmacokinetic study (50 mg/kg resulted in a peak concentration of 455 ng/mL), this may not have been the case for the parent drug. Overall, safety pharmacology studies were not comprehensive and possible effects on renal function and dependence/abuse potential were not investigated.

Pharmacokinetics

Following single intravenous (IV) administration, plasma clearance values were high in mice and rats but somewhat lower in rabbits and dogs (respectively 3.2, 3.2, 1.7 and 1.1 L/h/kg), with associated short half-life ($t_{1/2}$) values (1.5-2.9 h). Oral bioavailability using a 0.5% carmellose sodium vehicle was very low in mice and rats (5% and <1 %, respectively), with a higher value of 19% being obtained in rabbits and dogs, although absorption was much higher (39-56% or 62-86%, respectively based on plasma or urinary radioactivity). This is indicative of high first-pass metabolism and bioavailability would also be expected to be low for another vehicle used in many toxicity studies (2% potato starch), although there were no data for this. The lack of IV administration data in humans precluded determination of absolute bioavailability, but values of 54% and 36% have been estimated for poor and extensive CYP2D6 metabolisers, respectively (sponsor's Clinical Overview). Unlike humans in whom excretion was primarily urinary and mainly as metabolites, faecal excretion was more prominent in the experimental species, especially in rats in which extensive biliary excretion was shown.

Interspecies comparison of systemic exposures was not straightforward because of extensive and variable metabolism. As tabulated below (Table 3), systemic exposures to ILO and metabolite P95 (where administered) were sufficient, except for the ILO mouse and probably rat carcinogenicity studies. Daily dosing rather than twice a day dosing (bid) as proposed was used and a prominent sex-difference for rats was generally observed.

Data from the rat supplementary study, using the same strain and vehicle, suggested that the high-dose male exposure ratio in the rat carcinogenicity study may have been only approximately 1.5 (1.02 µg.h/mL at 24 mg/kg/day subject to a 0.66 fold dose adjustment). This contrasts with a higher estimated value of 5.3 for females.

There were no concurrent toxicokinetic studies in the ILO reproductive toxicity studies, in which the vehicle was 2% potato starch/mucilage, although exposures for the fertility/early embryonic development and pre/post-natal development studies could be estimated from the supplementary study. The high-dose of 36 mg/kg/day (reduced from 48 mg/kg/day in the latter study) would have been expected to result in an exposure ratio of 3.3 (males) or 11.9 (females) based on results with 24 mg/kg/day. Embryofetal development studies were conducted with Wistar rats and Himalayan rabbits, but there were no toxico-/pharmacokinetic data with these strains. Data from the Sprague-Dawley rat supplementary study suggests exposure ratios would be 0.5 (low-dose), 3.8 (mid-dose,

mean of increased and decreased dose-adjustment) and >35 (high-dose). The only rabbit data after PO administration was for a single dose using 0.5% carmellose sodium vehicle.

Concurrent toxicokinetic data were obtained in the embryofetal development study using metabolite P95 (see below), but concentrations and $AUC_{0\text{-}24\ h}$ values were very low compared with those obtained in non-pregnant females with the same dose in a 13 week toxicity study using the same rat strain (Han Wistar) and vehicle (0.5% carmellose sodium). The same assay was also used (High Performance Liquid Chromatography Mass spectrometry (HPLC/MS/MS) with electrospray ionisation), and the reason for the substantial (approximately 10x) difference is not clear, and it did not attract a comment by the sponsor's nonclinical expert. The sponsor's Nonclinical Overview and Toxicology Summary included safety margins calculated both in terms of doses in mg/m^2 and plasma AUC.

The supplementary study used for estimation of ILO exposures in the dog toxicity studies was characterised by high inter-animal variations. Additionally, different results were obtained in another study with the same doses, in which ILO was not always measurable with the low and mid-doses and which also showed high inter-animal variation. The high-dose exposure ratio in the latter study was 3.0 (Day 14) or 1.6 (Day 28) compared with 11.7 (Day 14) for the former study. These results probably reflect the high rate of metabolism in this species, and similar exposures to metabolite P95 (relative to ILO) were seen in the former study, while much higher exposures to P94 were seen in the latter study.

The major circulating metabolites after PO administration showed prominent species differences, as summarised below (based on plasma AUC) (Table 4). Duplicate entries refer to results from standard plasma assays or complete metabolic profiling.

Metabolite P88, which was a prominent plasma component in humans, was generally unmeasurable or present at very low concentrations in mice, rats and dogs, in contrast to rabbits. However, this reduced compound was in equilibrium with the oxidised form, ILO , and these results were consistent with an *in vitro* study in which human and rabbit S9 preparations showed a higher reduction/oxidation ratio. PO administration of P88 (S-enantiomer) resulted in plasma ILO in mice and dogs, and additionally, mouse plasma P88 was shown to be in the form of both the S and R enantiomers (S/R = 0.71 in terms of AUC). Chiral inversion was also noted in mice after PO administration of (S)P88, with a plasma S/R AUC ratio of 0.36. This contrasts with rabbits, dogs and humans in which P88 was virtually all or all in the form of the S-enantiomer.

The apparently minor human plasma metabolite P20.8 was identified as the cleavage product ILO N-dealkyl in the animal studies, and was a prominent metabolite in mice, rabbits and dogs, but it was not clear to what extent this was present in rats although it was generated by rat liver homogenate *in vitro*. Another apparently minor human plasma metabolite (P24.6) was the glucuronide conjugate of P36.3, a phenol derivative that was unlabelled after administration of radioactive carbon labelled (^{14}C)-labelled parent drug because of the loss of the labelled carboxyl moiety. This glucuronide conjugate was present in rabbit and dog plasma, listed under *ipso* substitution glucuronide.

Overall, the experimental animals were exposed to different metabolite mixtures compared with humans, and although exposure to the major human metabolite (P95) was probably adequate in dogs, this was not the case for mice and rats. To help address this issue, several toxicity studies were conducted in rats using PO administration of purified P95 (*General toxicity; Genotoxicity and carcinogenicity*).

Table 3. Animal: Human Exposure Ratios. Table continued across two pages.

Species	Duration (weeks)	Dose (mg/kg/day) and route	$AUC_{0\text{-}24\ h}$ (µg.h/mL) and sample day/week	AUC exposure ratio (ER)[&]
General toxicity: ILO				
Mouse^	13	5, 10, 20 PO	0.8 (m), 1.14, >2.92[$] (week 4)	1.7, 2.5, >6.3
Mouse*	104	2.5, 5, 10 PO	nc, nc, 0.64 (day 185)	-, -, 1.4
Rat^	13	4, 10, 25 PO	0.065, 0.21, 1.02 (m) 0.22, 0.82, 3.68 (f)	0.1, 0.4, 2.2 0.5, 1.8, 7.9
Rat^	26	12, 24, 48 PO	0.21, 1.02, 11.47 (m) 0.82, 3.68, 16.16 (f) (day 28)	0.4, 2.2, 25 1.8, 7.9, 35
Rat*	104	4, 8, 16 PO	Nd	
Dog^	13	4, 10, 25 PO	0.13, 0.52, 5.42	0.3, 1.1, 11.7
Dog^	52	6, 12, 24 PO	0.13, 0.52, 5.42	*ca* 0.3, 1.1, 11.7
Reproductive toxicity: ILO				
Rat	Fertility	4, 12, 36 PO	Nd	
Rat	Peri/ post	4, 16, 48/36 PO	Nd	
Rat	GD 7-18	4, 16, 64 PO	Nd	
Rabbit	GD 6-18	4, 10, 25 PO	nd	
General toxicity: metabolite P95				
Mouse	4	50, 250, 750, 1500	3.78, 72.7, <u>18.4, 38.7</u> (m) 3.75, <u>162, 185, 151</u> (f) (Days 1 (underlined)[#] or 27)	3.3, 64, 16.1, 34 3.3, 142, 162, 132
Rat	13	50, 200, 500 PO	2.42, 29.7, 115 (m) 1.58, 25.3, 132 (f) (Week 12)	2.1, 26, 101 1.4, 22, 116
Rat	13	100, 200, 500 PO	3.6, 7.6, 27.1 (m) 7.5, 18.9, 77.5 (f) (Week 13)	3.2, 6.7, 24 6.6, 16.6, 68
Rat	1-26	50, 500	3.0, 105 (m) 2.3, 265 (f) (Week 13, 26)	2.6, 92 2.0, 232

Species	Duration (weeks)	Dose (mg/kg/day) and route	$AUC_{0\text{-}24\ h}$ (µg.h/mL) and sample day/week	AUC exposure ratio (ER)&
Rat*	104	25, 75, 200 PO (m) 50, 150, 400/250 (f)	0.49, 2.99, 26.2 (m) 3.4, 9.8, 48.1 (f) (Week 26)	0.4, 2.6, 23 3.0, 8.6, 42
Reproductive toxicity: metabolite P95				
Rat	GD 6-17	20, 80, 200 PO	0.21 (n=1), 0.25, 2.35 (GD 17)	-, 0.2, 2.3

& compared with a human value of 0.464 µg.h/mL (0.232 µg.h/mL x 2) for ILO and 1.14 µg.h/mL (0.57 x 2) for metabolite P95; section 6.2.5

* carcinogenicity studies, # Day 1 only (subsequent 100% mortality)

^ from 2 or 4 week supplementary studies with similar doses, $ 4 week supplementary study high dose (HD) was 15 mg/kg/day

nc = not calculable, nd = no data, (m)=male; (f)=female; GD=gestation day.

Table 4. Major circulating metabolites after PO administration

Species	Compound	Quantitative ratios (reference)
Human	ILO, P88, P95	1: 1.5: 2.4 (ILO 522 0112)
Mouse	ILO, P95, RA*	1: 0.13: 15 (R01-1353)
	ILO, OR-P89-G, ilo N-dealkyl, P95, RA	1: 0.95, 0.8, 0.19, 5.0 (R01-1353)
Rat	ILO, P88, P95	1: 0.05: 0.03-0.06 (R01-1181)
	ILO, RA	1: 674 (R98-2214)#
Rabbit (f)	ILO, P88, P95, RA	1: 0.55, 0.17, 10.8 (R99-1190)#
	ILO, ilo N-dealkyl, OR-P95-G, OR-ilo-G, P95, RA	1: 2.2: 1.2, 1.7, 0.3, 14.9 (R99-1190)#
Dog	ILO, P95, RA	1: 0.78, 11.6 (R99-1189)#
	ILO, P95	1: 1-2.9 (R99-057)
	ILO, P94	1: 7.9-11.9 (0494-220)
	ILO, P94, P95, P88 carboxyl, ilo N-dealkyl, RA	1: 4.6, 2.7, 2.0, 1.9, 22.4 (R99-1189)#

* RA = radioactivity, # single dose studies. ILO = ILO , OR-P89/P95/ilo-G = open-ring P89/P95/ilo glucuronides

Toxicology

General toxicity

Elevated prolactin concentrations are a known effect of antipsychotic agents such as ILO which bind to dopamine D_2 receptors, and this was demonstrated in the rodent carcinogenicity studies, and in toxicity studies (males only) and a carcinogenicity study with metabolite P95. Small increases have been observed in the clinical trials, although these were apparently less than with haloperidol or risperidone (sponsor's C*linical Overview*). Besides oncogenic responses (*Genotoxicity and carcinogenicity*), mammary gland activity/secretion/vacuolation seen in the toxicity studies were almost certainly

prolactin-related. Uterine adenomyosis was also observed in the mouse carcinogenicity study, and may have been prolactin-related. The only other uterine findings were lower relative weights without histological correlates in the rat 13 week study. Doses used in the toxicity studies were sufficient to result in substantial impairment of body weight gains in rats (for example, by up to approximately 30% in the 26 week study), associated with variably decreased food consumption. Consequently some findings may have been indirect effects of poor nutrition or condition, including testicular tubular degeneration, prostatic inflammation and possibly bone marrow fatty infiltration which were prominent in the 4 and 26 week studies. Lymphoid necrosis, seen in the 13 week mouse study (but not the carcinogenicity study in this species) probably resulted from stress-induced elevated glucocorticoids, although there were no drug-related histological changes in the adrenals. Significant increases in relative adrenal weights were recorded in rats but without histological correlates or similar lymphoid necrosis being observed.

A number of haematological changes were seen, with the most consistent being small reductions in leukocytes, lymphocytes and platelets in rats, respectively by up to 32%, 34% and 14% in high-dose males in the 26 week study. However, these were generally associated with substantial impairment of body weight gain and were not apparent in dogs, suggesting a non-specific effect rather than indices of bone marrow toxicity. Bone marrow cellularity was significantly lower in male mice in the 13 week study, associated with both significantly lower proportions of lymphogenous cells and tendencies for lower circulating leukocytes and lymphocytes. However, bone marrow cellularity was unaffected in females, and in the other study in which it was examined (26 week rat study), high-dose cellularity was slightly reduced in both sexes, while the proportion of lymphogenous cells was either slightly higher (males) or reduced (females). Haematological examinations in the clinical trials apparently showed only minimal differences (sponsor's S*ummary of Clinical Safety*). A cautionary note regarding leukopenia is included in the proposed Product Information.

There was no indication of hepatotoxicity but hepatocytic vacuoles or enlargement were seen at histological examination in the dog studies, and electron microscopic examination respectively showed distended golgi apparatus or smooth endoplasmic reticulum proliferation. The latter appeared to be an adaptive hepatocytic hypertrophy, and although serum alanine aminotransferase (ALT) activities were also elevated in this study, changes were sporadic and not dose-related. Hepatocytic necrosis or bile duct changes were not observed. ALT was, however, apparently slightly elevated in the clinical trials, although increases were also seen with haloperidol and risperidone (sponsor's *Summary of Clinical Safety*).

The relatively benign histological findings suggest that ILO has little potential for toxicity, especially given an estimated high-dose drug exposure ratio of approximately 12 in the dog studies. Decreases in serum glucose were observed in rats, while in contrast slight hyperglycaemia occurred in the clinical trials (sponsor's *Clinical Overview*). Triglycerides were variably reduced in rats and dogs (by up to 50% in the 26 week rat study), which contrasts with an apparent lack of effect in the clinical trials.

Metabolite P95

As indicated above (*Pharmacokinetics*), doses used and systemic exposures achieved were much higher than with ILO , and in the case of mice proved to be excessively toxic. There were numerous drug-related findings in the rat studies, with a possible difference between the generally used Han Wistar strain and the Sprague-Dawley strain used in one 13 week study (numerous mortalities occurred with the latter but not the former at 500 mg/kg/day for 13 weeks). With the exception of the long term carcinogenicity and this 13 week study, histological findings generally appeared to be related to stress (adrenal

cortical hypertrophy), possible enzyme induction (thyroid weight increase or follicular hyperplasia in females) or prolactin. This hormone was shown to be elevated, at least in males, and related findings appeared to be enhanced mammary gland activity, vaginal mucification or reduced uterus/vagina keratinisation, prostatic/testicular atrophy or prostatic inflammation, ovarian interstitial cell hyperplasia or reduced corpora lutea degeneration and reduced pituitary pars distalis eosinophilia.

Thyroid findings were not prominent, but may have been secondary to hepatic enzyme induction although this was not measured for P95. There was little or no evidence of enzyme induction in rats treated with up to 80 mg/kg/day ILO for 2 weeks in a special study, but hepatocytic hypertrophy with proliferation of smooth endoplasmic reticulum was seen in the longest duration dog study. However, the thyroids were unaffected in the long term rat carcinogenicity study with P95, although centrilobular hepatocytic hypertrophy was present in both sexes.

Mortalities in Sprague-Dawley rats in the 13 week study were associated mainly with urinogenital disease and these individuals additionally showed liver bile duct hyperplasia (also seen survivors) and hepatic necrosis suggesting the kidneys and liver were target organs. The lethal dose of 500 mg/kg/day not only resulted in high systemic P95 exposures (exposure ratios of 24 in males and 68 in females) but based on results of an IV pharmacokinetic study, high concentrations of metabolite conjugates. Further, this represented a high absolute drug dose, that is 3000 mg/m^2/day compared with the proposed maximum clinical dose of 15.8 mg/m^2/day (24 mg/50 kg x 33), and there was some evidence of overloading of excretory routes, that is, sporadic urinary crystals and crystals in the main bile ducts. Excretion data for rats after P95 administration was only obtained for IV administration, and was overwhelmingly (>95%) via the faeces after single dosing. Excluding putative prolactin-related changes there were few effects of treatment with the low- or mid doses of 100-200 mg/kg/day, resulting in P95 exposure ratios of approximately 3-7 (males) or 7-17 (females). In the comparable study in Han Wistar rats, there were no drug-related mortalities or direct toxicity, although as tabulated above, P95 exposure ratios were very high (>100 with the high-dose).

Non-neoplastic findings in the (Han Wistar) rat carcinogenicity study, in which high-doses were 200 mg/kg/day (males) or 400 reduced to 250 mg/kg/day (females), included prominent nephrotoxicity associated with elevated serum urea, and hepatotoxicity. The latter included liver bile duct hyperplasia/peribiliary fibrosis, hepatic necrosis and bile duct epithelial hyperplasia and inflammation but increases were restricted to HD females initially treated with a lethal high-dose of 400 mg/kg/day. It was difficult to determine the exact dose at which nephrotoxicity was apparent, but histological changes were largely confined to the same dose group, although slightly elevated serum urea was also measured in mid-dose males and females, and females for all dose groups showed significantly increased urinary volumes. Two high-dose female premature deaths also showed renal papillary birefringent crystals which may be related to excretory overload, and excluding this and the high-dose male group, both of which showed increased mortalities, P95 exposure ratios were up to 2.6 (males) or 8.6 (females).

As with ILO , lower glucose was also seen in the carcinogenicity study, while slightly elevated phosphorus (also noted in the 13 week Sprague-Dawley rat study) probably reflected altered renal function.

Overall and with the proviso that human and experimental animal metabolite patterns differed, there were no findings to preclude approval of this application. Excluding clinical signs, the No Observable Effect Level (NOEL) values and associated safety margins based on AUC were either low or not established, although this was often related to impaired body weight gain or putative effects of prolactin. For example the low-dose in the longest

duration rat ILO study (exposure ratios of 0.5 in males, 1.8 in females) resulted in impaired weight gain, reduced serum glucose and triglycerides and mammary gland changes.

Genotoxicity and Carcinogenicity

ILO was positive in an *in vitro* chromosomal aberration assay in Chinese hamster ovary cells, in two separate studies from the same laboratory; either only in the presence of S9 activation (≥89 μg/mL) or both in the presence or absence of S9 (≥79 μg/mL). The sponsor's Nonclinical Overview suggested that ILO was inactive except under strongly cytotoxic conditions but this was not the case as concurrent cell numbers at concentrations giving positive responses were decreased by 0-68%. An earlier study at a different laboratory was also conducted but with negative results, although much higher concentrations were tested (250-1000 μg/mL) and cytotoxicity appeared to be low. A similar concentration range (100-1000 μg/mL, equivalent to 0.23-2.3 mM) was also tested in a forward mutation assay in Chinese hamster ovary cells with toxicity not being observed.

The significance of the positive responses is difficult to determine but they were not consistent with negative results in the *in vivo* micronucleus tests carried out in mice (2 studies) and rats (hepatocytes examined). Other adequate genotoxicity tests did not suggest any genotoxic potential and overall, ILO is considered to be non-genotoxic. Additionally, adequate studies with the major human metabolite P95 also gave negative results, and it is noteworthy that concentrations used in the *in vitro* chromosomal aberration assay in Chinese hamster V79 cells (up to 250 or 300 μg/mL) were not cytotoxic. Concentrations tested were limited by precipitation.

Long-term carcinogenicity studies were conducted with ILO in mice and rats, although as noted above (*Pharmacokinetics*), drug exposure ratios based on plasma AUC were low, especially in mice and male rats (estimated values). This contrasts with the high P95 exposures obtained in a rat study with this major human plasma metabolite. However, the ILO high-dose could not be increased in mice because of increased mortality which necessitated early termination at 82 weeks in order to leave sufficient numbers of survivors. Likewise, the rat high-dose could not be increased because of excessive impairment of body weight gain (by 48% in males and 38% in females), associated with lower food consumption. Appropriate statistical analysis was conducted, but only the rat study with metabolite P95 included a separate statistical report.

There were no clear indications of oncogenic responses in mice, although the incidence of female mammary gland adenocarcinomas was markedly higher in the low-dose group (12/60 versus 1/120 controls). Similar increases have been observed with other antipsychotic drugs, for example risperidone, and ascribed to elevated prolactin levels (Risperdal PI). Consistent with this, drug-related serum prolactin elevations were demonstrated to a similar extent with all ILO doses in the mouse study (by approximately 4 fold). However, an increased incidence only with the low-dose would not be expected and this finding may have been incidental, although it should be mentioned in the PI.

In the rat study a significant trend for pancreatic islet cell adenomas was observed in both sexes, but at $p<0.05$ rather than the more appropriate level of $p<0.005$ for common tumours. It is of interest however, that endocrine pancreatic tumours were increased in male rats treated with risperidone (Risperdal PI), an effect also ascribed to elevated prolactin. This hormone was shown to be elevated with all doses in the ILO study, by up to approximately 5 fold (males) and 4 fold (females). Additionally, pancreatic islet cell adenomas were significantly increased in high-dose male rats in the long term carcinogenicity study with P95 ($p=0.005$ for trend, $p=0.007$ by pairwise comparison). The

other significant oncogenic findings in this P95 study were increased incidences of pituitary pars distalis adenomas with all doses in males (p=0.003 or <0.001), and both tumour types were probably related to the demonstrated elevations in prolactin with all doses in both sexes (by up to 17-18 fold). It is noteworthy that increased P95-related cellular proliferation, as quantified by labelling indices, was seen in the alveolar and ductal mammary gland (both sexes), pituitary (males) and pancreas (females) in a 26 week rat toxicity study.

Overall, the lack of genotoxicity and demonstrated increases in prolactin suggest the oncogenic findings are hormone related and that ILO and its metabolites are without effect. Although there is no reason to expect a different result, the potential oncogenicity of P95 has not been fully explored due to the lack of a corresponding study in the mouse.

Reproductive toxicity

Embryofetal development studies were conducted with ILO in Wistar rats and New Zealand White (NZW) rabbits, with no evidence of teratogenicity and only skeletal (rats) or visceral (rabbits) variations being seen at fetal examination even with the high-doses which elicited abortions and/or resorptions. As noted previously (*Pharmacokinetics*), the estimated high-dose ILO exposure ratio in rats was >35, while there were insufficient data to determine a corresponding value for rabbits, a deficiency in this study. Doses based on body surface area were 24, 96 and 384 mg/m^2/day (1.5, 6 and 24 times that expected in humans with the maximum recommended dose) in rats, with corresponding rabbit values of 60, 150 and 375 mg/m^2/day (3.8, 9.5 and 24 times the human value). Excluding minor reductions in skeletal ossification, embryofetal lethality (abortions, resorptions) and retarded development (reduced fetal weights) occurred only with the high-dose which exhibited maternal toxicity (one death and reduced body weight gain and food consumption). Fetal visceral abnormalities were not observed in a fertility and early embryonic development study, with caesarian sectioning on gestation day 20, although skeletal examinations were not conducted. The high-dose of 36 mg/kg/day (216 mg/m^2/day) would have achieved an expected exposure ratio based on AUC of 3.3 (m) and 11.9 (f) in this study; the 216 mg/m^2 dose was 13.6 times the human mg/m^2 value.

Interpretation of adverse effects of treatment in rabbits was not so straightforward, in part because treatment was initiated on gestation day 6, which may include the time of implantation. The high-dose was lethal, resulting in one maternal death, while maternal body weight losses (associated with lower food consumption) were observed with all doses during the first week of treatment. Excluding a higher incidence of a fetal visceral variation in the high-dose group, adverse reproductive effects were restricted to reduced implantations and live fetuses in this group, and tendencies for higher implantation losses in this and the mid-dose group. A relationship to treatment appeared likely because of their group distribution and the early initiation of dosing, in which case the NOEL would be the low-dose.

An additional study with metabolite P95 was conducted in Wistar rats, with no evidence of effects on embryofetal development although the high-dose of 200 mg/kg/day resulted in a relatively low exposure ratio based on AUC (2.3). It was not clear, however, why this was so much lower than that obtained in a 13 week toxicity study with non-pregnant rats. Unlike rats, metabolite P95 was a substantial circulating metabolite in rabbits (0.17-0.3 times that of the parent drug based on AUC), although to a much lower extent than in humans (corresponding ratio of 2.4 times).

ILO treatment of Sprague-Dawley rats from prior to mating resulted in prolonged dioestrus with associated decreased fertility (pregnancies/co-habitation), although re-pairing with untreated females showed that male fertility was only slightly lower (91%

versus 100% for the controls), which was at variance with the report text which noted 100% fertility. Additional adverse effects noted in this study, which included both gestation day 20 caesarian and littering phases, included reduced corpora lutea and implantations, and increased stillborn pups and their survival over 4 days. The latter was associated with necropsy finding of empty stomachs, which may be related to impaired maternal care resulting from pharmacological activity. However, subsequent pup behaviour and development to maturation, including reproductive function, were unaffected by maternal treatment. Gestation times were slightly higher in mid- and high-dose dams but parturition appeared to be unaffected. Excluding clinical signs, the NOEL for females was the low-dose of 4 mg/kg/day which would be expected to achieve only a very low systemic exposure (estimated exposure ratio of 0.5 based on AUC). A somewhat higher ratio is obtained based on dose in terms of body surface area (24/15.84 $mg/m^2/day = 1.5$).

Numerous untoward effects of treatment were observed in a peri-/post-natal study, including increased gestation length, prolonged parturition, increased stillborn pups with lower weights and reduced offspring survival to culling on Day 4 and to weaning. Additionally, 3 high-dose dams were killed at or around the time of parturition. However, post-weaning offspring development, including reproductive function at maturity, were unaffected by maternal treatment. Some if not all of these adverse effects may be pharmacologically-mediated and prolonged parturition with increased stillbirths have been reported with the antipsychotic olanzapine (Zyprexa PI). Reduced pre weaning pup growth and survival appeared to reflect impaired maternal care, with the high-dose being reduced in early lactation due to maternal sedation and additionally increased incidences of empty pup stomachs were observed at necropsy. Excluding maternal clinical signs, the low-dose of 4 mg/kg/day also elicited increases in the total number of stillborn pups and incidence of dams in which these occurred. A NOEL was therefore not established (quoted as the low-dose in the report), while by contrast, this dose was the NOEL in the fertility and early embryonic development study (above).

Impurities

No specific studies were conducted with the specified impurities and degradation products.

Three impurities with limits in the Active Pharmaceutical Ingredient (API) specification exceeded the ICH qualification threshold of 0.15%. These were designated Q2, Q4 and Q7, and although these were not investigated in specific studies, all three compounds were present in ILO batches used in the toxicity studies. These were considered to have been adequately qualified. There are no degradants in the finished product specifications that exceed the ICH qualification guidelines.

Nonclinical Summary and Conclusions

- *In vitro* receptor binding assays showed that ILO had high affinities for human and rat dopamine, α-adrenergic and serotoninergic receptors. Functional studies showed antagonism at these receptors. *Ex vivo* studies showed marked inhibition of ligand binding to $5HT_{2A}$ receptors and weaker inhibition of binding to D_2 receptors, consistent with characteristics of atypical antipsychotic drugs. Results from *in vivo* studies were consistent with the antagonistic activity of ILO at serotoninergic and dopamine receptors. ILO was active in animal models of antipsychotic activity, and there was some evidence for anxiolytic activity. The P88 carbonyl reduction metabolite showed similar or slightly weaker binding affinities than the parent drug, while the P95 methoxybenzoic acid metabolite showed high affinity only for $5HT_{2A}$ and adrenergic α receptors.

- Safety pharmacology studies were not comprehensive but *in vitro* tests showed inhibition of hERG currents by ILO (50% inhibitory concentration (IC_{50}) = 29 nM, equivalent to 12.4 ng/mL, at room temperature) but only minimally by the main human plasma metabolite, P95 (IC_{50} >4 μM). Canine Purkinje fibre action potential duration (APD_{90}) was also significantly prolonged by ≥0.1 μM ILO , but not by P95. Decreases in rat and dog blood pressures, associated with lower total peripheral resistance in dogs, were observed in *in vivo* studies and probably related to demonstrated antagonism of vascular α_1-adrenergic receptors. Dependence or abuse potential were not investigated.

- The pharmacokinetics of ILO in the main toxicity species (rat, dog) were characterised by low bioavailability, especially in rats (<1%), high first pass metabolism and plasma clearance values (respectively 3.2 and 1.7 L/h/kg) and primarily faecal excretion. Substantial biliary excretion was demonstrated in rats. Numerous circulating metabolites were identified in all species examined, with prominent differences being observed, including particularly low levels of the main human metabolite P95 in rats. *In vitro* experiments with human microsomal preparations and recombinant CYP isoforms suggested that CYP2D6 and to a lesser extent CYP3A4 were important for ILO metabolism. ILO inhibited CYP2D6 and CYP3A4/5, with K_i values of approximately 1.4 μM and 2.5 μM, respectively, (equivalent to approximately 600 and 1100 ng/mL), but metabolite P95 showed little or no activity.

- ILO *in vitro* protein binding was high in rat, dog and human plasma (approximately 88%, 86% and 93%, respectively, at 20 ng/mL in one study), as was the binding of metabolite P95 (corresponding values of approximately 91%, 70% and 85%, respectively, at 10 ng/mL). Several *in vivo* tissue distribution studies in rats were included, with IV and/or PO [^{14}C]-ILO administration. Radioactivity was widely distributed with salient findings of peak brain concentrations similar to or above those for blood and evidence for melanin binding in pigmented rats. Following [^{14}C]-P95 administration, radioactivity was highest in bile and minimal or undetectable in brain. Fetal labelling was low after [^{14}C]-ILO administration to pregnant rats and rabbits, and was not demonstrated after [^{14}C]-P95 administration to rats. *In vitro* experiments showed ILO and metabolite P88 inhibited p-glycoprotein (50% inhibitory concentration (IC_{50}) = 0.88 μM and 3.7 μM, respectively, in one experiment), while metabolite P95 was a weak substrate.

- Because of the low concentrations of circulating metabolite P95 in rats, the toxicity profile of this agent was investigated in several studies. These included repeat-dose toxicity studies in mice (4 weeks) and rats (2 studies of 13 weeks and one of 1-26 weeks), genotoxicity and a long term carcinogenicity study and an embryofetal development study in rats.

- The main repeat-dose toxicity studies with PO ILO were of 13 and 26 weeks duration in Sprague-Dawley rats (respectively to 25 and 48 mg/kg/day), and 13 and 52 weeks duration in beagle dogs (to 24-25 mg/kg/day). The high-doses in the longest duration studies achieved estimated plasma exposures based on AUC that were >20 (rats) and >11 (dogs) fold that expected in humans with the maximum recommended dose, although dog values were particularly variable. A 13 week PO study in CD mice was also carried out.

- Besides clinical signs, impaired body weight gain and changes putatively ascribed to stress (lymphoid necrosis) and elevated prolactin (such as mammary gland activation), there were few significant effects of treatment. Higher PO doses used (and drug exposures achieved) in the studies with P95 resulted in excessive mortalities in

mice and Sprague-Dawley rats but not in Han Wistar rats. The rat mortalities were mainly associated with urinogenital disease and also showed liver bile duct hyperplasia, possibly consequences of excretory overload. Nephrotoxicity and hepatotoxicity, including bile duct changes, were also noted at a lethal dose in Han Wistar rats in a long term carcinogenicity study with P95. Elevations in prolactin were demonstrated in this study and in mouse and rat carcinogenicity studies with ILO .

- A special 7 day study did not show any evidence of ototoxicity in guinea pigs, while results of *in vitro* assays suggested that ILO (but not metabolites P88 and P95) may show some phototoxicity. There was no indication of specific immunotoxicity in another special 4 week study in Sprague-Dawley rats at doses that achieved exposures based on plasma AUC that were 4-11 times (ILO) or 39-80 times (P95) those expected in humans with the maximum recommended dose.
- ILO was positive in an *in vitro* test for chromosomal aberrations in two studies, but the biological significance of this was not clear and results were not consistent with negative findings in *in vivo* micronucleus assays in mice and rats. Metabolite P95 did not show any genotoxicity in adequate tests. Long-term carcinogenicity studies were adequate and although ILO high-doses resulted in relatively low drug exposures based on plasma AUC they elicited increased mortality (mice) or excessive impairment of body weight gain (Sprague Dawley rats).
- Noteworthy oncogenic findings with ILO were increased mammary gland adenocarcinomas in female mice but only with the low-dose, and increased pancreatic islet cell adenomas in male and female rats. These pancreatic tumours were present in the controls and the small increases observed did not reach appropriate levels of statistical significance. Pancreatic islet cell adenomas were significantly increased in high-dose males in the P95 study in Han Wistar rats, while pituitary pars distalis adenomas were increased in males with all doses and these findings are most likely related to the demonstrated elevations of prolactin. A long term carcinogenicity study with P95 was not conducted in mice.
- Embryofetal development studies did not show any teratogenicity, with doses that resulted in high drug exposures based on estimated plasma AUC (Wistar rats) or body surface area (Wistar rats, NZW rabbits). An embryofetal development study was also conducted with P95 in Han Wistar rats, with no adverse fetal or maternal effects (other than clinical signs). The high-dose (200 mg/kg/day), however, achieved exposure to this metabolite based on plasma AUC that was only approximately 2 fold that expected in humans with the maximum recommended dose.
- Fertility and early embryonic development and peri-/postnatal studies in Sprague Dawley rats revealed a number of untoward effects that were probably related to pharmacological activity. These included prolonged dioestrus and reduced fertility in females, a tendency for slightly lower fertility in males, increased gestation time, prolonged parturition and increased stillborn pups and reduced pup survivals to weaning. However, post-weaning development, including reproductive performance at maturity, was unaffected by maternal treatment.

Conclusions and Recommendations

ILO exhibited receptor binding and functional characteristics of an atypical antipsychotic drug and would be expected to be efficacious for the proposed indication, although the extent to which it compares with other registered drugs can only be determined from the clinical studies. There were no findings in the adequate toxicity studies conducted in rats

and dogs to preclude approval of registration. Studies included investigation of the toxicity of the main human plasma metabolite P95, which was appropriate as this compound was not present in significant amounts in rodents. It should be noted that an *in vitro* study suggested some potential for ILO to exhibit phototoxicity, although this was not investigated in experimental animals.

The results of the single assay in which ILO showed genotoxicity (chromosomal aberrations in Chinese hamster ovary cells) appeared not to be biologically significant and overall, ILO and metabolite P95 were not genotoxic. Neoplastic findings in the long term carcinogenicity studies were probably related to hyperprolactinaemia which was demonstrated in both sexes. Prolactin is characteristically elevated by antipsychotic agents, and several registered drugs show associated neoplastic changes in long term carcinogenicity studies.

Amendments to the Product Information document were also recommended by the nonclinical evaluator but these are beyond the scope of this AusPAR.

IV. Clinical Findings

Introduction

The sponsors seek an indication for the treatment of psychotic symptoms in schizophrenia rather than schizophrenia per se. This indication is inconsistent with indications for all other currently available atypical antipsychotic pharmacotherapies, which carry an indication at the disorder level "Schizophrenia" rather than specifying symptoms within this disorder. There is no clear rationale for such an indication and it is not consistent with EU guidelines. Thus this evaluation proceeds on the assumption that the indication is for schizophrenia, not a narrower set of symptoms.

In support of this application, data for seven safety and efficacy trials was received. There were four short term randomised, placebo (PBO) and active-controlled, double-blind, efficacy studies (3000, 3101, 3004 and 3005) conducted between 1998 and 2006. Of these, 3000 and 3004 have long term double-blind phases and three were three long term double-blind studies (3001, 3002 and 3003). The dose range for which approval is sought is 12 – 24 mg a day.

This was a complete application and included full reports of the clinical trial development process.

Maximum single dose tolerable in healthy volunteers was found to be 3 mg/day, and the majority of PK studies use this dose. In patient populations doses early studies examined low doses ranging from 4 to 8 mg/day and the dose range increased progressively in subsequent studies up to a maximum of 24 mg/day. Phase three trials ranged in dose from 4 mg/day to 24 mg/day.

PK/PD, safety and tolerability studies have been conducted in healthy volunteers and patients, in renal and hepatically impaired patients and in elderly patients with dementia. Most Phase III studies were multi-centre and included European, North American, South American, Asian and Indian sites. Despite this geographic variability, the majority of study participants were Caucasian in most studies. There have been no paediatric trials, however the sponsor undertook, at the request of the US FDA, to conduct such a trial which is scheduled for completion in 2014. There have been no Phase III trials in elderly patients.

The clinical program was not conducted in Australia and the TGA has not provided guidance on the conduct of that program to the sponsor.

All studies reviewed were designed and conducted in accordance with the Declaration of Helsinki and the relevant regulatory guidelines including the US Code of Federal Regulation governing protection of human subject, Institutional Review Boards, and the obligations of clinical investigators and with the International Conference on Harmonisation Guidance for Good Clinical Practice (GCP).

Pharmacokinetics

Introduction

Full PK documentation has been submitted as required.

PK data was derived from 37 studies conducted by the sponsor over the development history of the agent. Main studies include: two studies examining PK parameters in healthy volunteers, two Phase II studies examining PK parameters in patients with schizophrenia, three Phase III studies in patients with schizophrenia, 4 bioequivalence (BE) studies, 2 food effect studies, 2 ADME[4] studies, 1 study each renal of impairment and hepatic impairment, cytochrome P450 (CYP) 2D6 inhibition and fluoxetine interaction, 2 electrocardiogram (ECG) studies (1 in healthy volunteers and 1 patients with schizophrenia) and 1 QTc[5] study in patients with schizophrenia, 1 study of poor and extensive CYP2D6 metabolisers in HV, and 1 dose proportionality study in HV. Relevant results and supporting studies will be summarised in text.

Early studies use the prototype formulation, while the remainder use the Final Market Formulation either as tablet or in an over-encapsulated form. The BE studies show that for practical purposes the three formulations are bioequivalent. The BE studies carried out comparing the different formulations are described below.

The main metabolic pathway is CYP2D6 and thus individuals who are poor CYP2D6 metabolisers will differ in PK parameters from normal (extensive) metabolisers. Poor and extensive metabolisers can be identified by genotyping, and differences between poor and extensive metabolisers are detailed below where data is available.

The Clinical Overview provided by the sponsor was an adequate summary of the program of PK evaluation. Given the large number of studies conducted, the identification of the smaller set of studies to discuss in the sponsor's Clinical Overview with respect to characterising the PK parameters of ILO appears non-biased and representative.

PK studies were designed and appear to have been conducted in compliance with GCP.

Methods

Analytical methods

Analytical methods for determining PK parameters for ILO and its two main metabolites P 88 and P95 in human plasma and urine were determined in Studies DMPK(US) R99-720 and DMPK(US) R99-2297, DMPK(US) R98-3042 , ILO 522 0108/DMPK(US) R99-663. Those studies determined that a solid-phase extraction procedure and analysis of the extract by electrospray ionization-liquid chromatography/tandem mass spectrometry (ESI-LC/MS/MS) was suitable for the routine analysis of Ilo, its major active metabolite

[4] Pharmacokinetic studies of **A**bsorption, **D**istribution, **M**etabolism and **E**xcretion (ADME).

[5] The QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias and sudden death. The QT interval is dependent on the heart rate (the faster the heart rate, the shorter the QT interval). To correct for changes in heart rate and thereby improve the detection of patients at increased risk of ventricular arrhythmia, a heart rate-corrected QT interval *QTc* is often calculated.

P88 and P95 in human plasma and urine. This method was found to be specific for the three analytes within the predefined criteria for acceptance (apparent peak area for ILO , P88, and P95 in zero samples ≤ 20% of mean peak area at the lower limit of quantification [LLOQ]). The anticipated nominal level of quantification was 50, 100, 200 pg/mL for ILO , P88 and P95 respectively in plasma and 52, 99, 400 pg/mL for ILO , P88 and P95 respectively in urine. Unless otherwise noted, this method was used in all human PK/PD studies.

Pharmacokinetic data analysis

Note that 3 mg was the maximum tolerable single dose in healthy volunteers and all PK studies use this or a lower dose.

Absorption

In the main Absorption Distribution Metabolism Excretion (ADME) study, a single 3 mg dose of ILO administered orally to normal healthy volunteers reached a maximum plasma concentration (C_{max}) of 1 to 5 ng/mL within 2 to 3 hours (t_{max}) (Study ILO 522 2301). Based on urinary excretion of radioactivity in man, absorption was at least 56% of a 3 mg radioactive carbon labelled [^{14}C] ILO dose (2301).

Bioavailability & Bioequivalence

There have been no studies of absolute bioavailability. Estimated absolute bioavailability, based on human ADME study (2301), is 36% in extensive CYP2D6 metabolisers and approximately 56% in poor CYP2D6 metabolisers.

The bioequivalence of the dose form proposed for marketing, FMF-T, and the clinical service formulation (prototype) used in the early PK studies has been demonstrated (ILO 522 110). Additionally the bioequivalence of the FMF-T and the over-encapsulated version of the FMF-T (FMF-C) used in Phase III blinded trials, some of which also provided PK data, has also been demonstrated (ILO 522 110, 1002).

Influence of food

Two specific food studies have been conducted: one using the prototype formulation (103), and one using the FMF-T (IL0522 0105). In summary, food prolonged t_{max} from a median of 2 hours in the fasted state to a median of 3 hours in fed state. Differences in other PK parameters are small (ILO (fasted:fed): C_{max} (ng/ml) : 3.3±1.5 versus 2.8±0.8; area under the plasma concentration time curve from time zero to infinity ($AUC_{0-\infty}$) (ng/ml.h): 44.4±19.7 versus 47.5±19.1; P88 C_{max} 2.9±7.8 versus 2.7±0.5, t_{max} 4 versus 6 h, $AUC_{0-\infty}$: 71.8±24.4 versus 74.5±21.2, P95: C_{max}: 3.6±1.8 versus 2.7±1.4, t_{max} 6 versus 12, and $AUC_{0-\infty}$ 130.9±52.1 versus 121.7±48.2) and unlikely to be clinically relevant. The earlier study, performed with the 3 mg of the prototype formulation (Study ILPB103) produced similar results if somewhat lower values in certain parameters (fasted versus fed; t_{max} 2.2 versus 4.3 h, C_{max} (ng/ml) : 2.32 versus 2.0; $AUC_{0-\infty}$ (ng/ml.h): 27.6 versus 31.2). Thus, with respect to absorption and PK characteristics, ILO can be taken with or without food.

Distribution

Single-dose PK was examined in 13 separate single dose studies in healthy volunteers, conducted under similar experimental conditions. Without titration a single dose of 3 mg was the maximum tolerated dose in healthy volunteers and dose range in studies is between 1 and 3 mg.

The three largest studies were ILO 522 0104 (19 subjects all genotyped as extensive CYP2D6 metabolisers), ILO 522 0105 (26 subjects), and ILO 522 0110 (24 subjects). Other

studies are smaller and generally conducted to examine specific questions such as the effect of food or bioequivalence. These studies will be addressed in the relevant sections.

In summary, at a single oral 3 mg dose administered to healthy volunteers, ILO reached a maximum (C_{max}) of 1 to 5 ng/mL within 2 to 3 hours (t_{max}), from which plasma concentration of ILO declined slowly and in some instances concentrations of 0.05 to 0.1 ng/mL were detectable for up to 72 h. In general the decline was bi-exponential in nature, with a terminal elimination half-life of 10 to 30 hours. Based on estimates from the area under the curve, the total apparent oral clearance is 50 to 200 L/h, apparent volume of distribution is 1500 to 3500 L and renal clearance is 0.3 to 0.9 L/h.

For the main metabolites, C_{max} values of 2 to 4 ng/mL and 3.5 to 5 ng/mL were reached in 2.5 to 4 h and 4 to 6 h for P88 and P95, respectively. Exposure over time for both metabolites declined non-exponentially. For P88, C_{max} was similar to parent drug, while exposure ($AUC_{0-\infty}$) was approximately two fold higher, while for P95, C_{max} was 1.5 fold higher, and exposure was 4.5 fold higher than the parent drug. Both metabolites have a slightly longer terminal half-life than the parent drug. Apparent oral clearance and apparent volume of distribution are within the same ranges as ILO for P88 and p95, while renal clearance was somewhat higher (45 to 53 and 66 to 75 L/h for P88 and P95 extensive and poor metabolisers, respectively).

Elimination

Excretion

Two ADME studies (ILO 522 2301 and 105) examine excretion.

Overall, the amount of unchanged parent compound in the excreta accounts for less than 1% of total radioactivity administered in the radiolabelled ADME study, indicating extensive metabolism. The main route of elimination of metabolites in humans is urine, with biliary excretion to faeces contributing a minor portion only. This differs from animal studies, where biliary excretion is the main route in the rat and dog.

In ADME study (ILO 522 2301) in six subjects (two PMs), 89.5% of the dose was recovered in the excreta and was considered complete. The main route of elimination in humans is urine (70% of the dose in EM, 61% in PM), with biliary excretion to faeces contributing a minor portion (21% in EM, 25% in PM). Study ILPB105 was a small study in 3 subjects only. It did not distinguish by poor and extensive metabolisers but had comparable findings.

Excretion of metabolites P88 and P95 also varied in extensive and poor metabolisers. In extensive CYP2D6 metabolisers, the metabolite P95 and its glucuronide accounted for about 30% of the dose and metabolite P88 for about 5% of the dose found in excreta. In poor CYP2D6 metabolisers, the proportion of P95 and its glucuronide is lower (about 15%), with a somewhat larger proportion of P88.

Metabolism

Animal studies identified multiple metabolic pathways and many metabolites circulating in the blood. Subsequent studies in humans confirmed that the main metabolic pathways were essentially the same as those identified in animals**,** with three being of practical importance:

1. CPY2D6 which leads to formation of the most abundant metabolite in systemic circulation, P95.
2. A reduction pathway leading to the formation of second most abundant metabolite, P88.

3. CYP3A4 pathway which produces metabolite P89 and probably other metabolites present in low quantities in circulating blood.

At steady state, over a dose range of 2 – 12 mg twice a day (bd) in patients with schizophrenia (Study 0112) the total systemic exposure (AUC) to P95 is about 2.5 times that of ILO and for P88 about 50% higher than ILO. P95 does not cross blood-brain barrier and as so can be considered inactive in the central nervous system (CNS), whereas P88 does cross the blood-brain barrier and so is considered to be an active metabolite.

P89 is present in only small quantities (2301), however co-administration of a CYP3A4 inhibitor (ketoconazole) results in a modest (about 50%) increase in exposure to ILO and P88 (ILO 522 0107)**.** This is discussed below in the Interactions section, as is the effect of CYP2D6 inhibitors including fluoxetine (ILO 522 0108) and dextromethorphan (ILO 522 0104).

Individuals who are poor CYP2D6 metabolisers and those with hepatic impairment have, on average, moderately higher plasma levels of ILO and P88 than extensive metabolisers and those with normal liver function. Renal impairment, however, does not appear to affect metabolism of ILO or its metabolites (see below).

Pharmacokinetics of metabolites

Pharmacokinetic properties of the two most abundant metabolites, P88 and P95, were examined in the majority of clinical studies of the parent compound and are included in relevant sections of this report. PK/PD parameters of P88 and P95 in special populations are also addressed below.

Consequences of possible genetic polymorphism

Some 7-10% of Caucasians are poor CYP2D6 metabolisers. Poor and extensive CYP2D6 metabolisers can be identified by genotype in polymorphisms in CYP2D6 pathway genes. Studies 2301 and ILO 522 0104 used genotyping to examine PK differences for Ilo, P88 and P95 in poor and extensive metaboliser in healthy volunteers. Results of the two studies showed similar patterns. ILO 522 0104 was the larger of the two studies and it found that the exposure to ILO and metabolite P88 were significantly higher in poor CYP2D6 metabolisers ($AUC_{0-\infty}$ by 57% and 95%, respectively) compared to extensive metabolisers. Peak plasma concentrations of P88 were 44% higher than those of extensive metabolisers. However, in this study, peak concentrations of ILO were only marginally lower in poor CYP2D6 metabolisers compared to extensive metabolisers (2.26 versus 2.79 ng/ml). In a subsequent population PK study (VP-VYV-683-3101), increased exposure at steady state of ILO was observed in poor metabolisers, as would be expected.

In ILO 0104, poor metabolisers had significantly lower plasma concentrations of metabolite P95 compared to extensive metabolisers ($AUC_{0-\infty}$ was 80% lower and C_{max} was 85% lower). There was little difference in the amount of unchanged ILO excreted in urine in extensive and poor metabolisers (0.45% and 0.70% of the administered dose, respectively). With respect to the metabolites, the amount of P88 in urine was higher in poor metabolisers (8% versus 4.2% of the administered dose) and the amount of P95 excreted in urine approximately 76% lower in poor versus extensive metabolisers (4.5 versus 19.2% of the administered dose).

The draft PI notes that ILO and the active metabolite P88 concentrations are increased in poor CYP2D6 metabolisers and clinical evaluation will need to assess the metabolic status of patients and reduce dosage by up to half depending on clinical assessment. The draft PI notes that laboratory tests are available to identify poor metabolisers but does not specifically refer to or recommend routine genotyping.

Dose proportionality and time dependency

Dose proportionality at steady state was examined in target populations in Study ILO 522 0112.

This was a two-phase, open-label, steady-state PK study evaluating the dose proportionality of ILO 2, 4, 8, and 12 mg bd, in patients with schizophrenia. The study was conducted at a single centre in the US, with the first patient receiving study drug in April 2000 and the last patient completing the study in October 2000. Patients were male and female, provided informed consent and had vital signs within designated limits. The average age was 35.4±8.9 years, and subjects had a diagnosis of schizophrenia or schizoaffective disorder. Thirty-one patients were enrolled in the study, 28 had at least one PK assessment and 16 completed the PK study.

There was a 21 day screening period and a 38 treatment period. There were four phases in the study, with additional titration periods included. The dose was increased from 1 mg bd up to 12 mg bd over a 31 day period.

PK parameters were assessed for ILO and metabolites P88 and P95 including: area under the plasma concentration time curve over a dosing interval (AUC_T), $AUC_{0-\infty}$, C_{max}, t_{max}, and $t_{½}$, oral clearance (CL_t/F) and apparent volume of distribution (V_z/F) were calculated for ILO only. PK parameters for ILO and metabolites were log-transformed and evaluations of dose proportionality were performed on AUC_T, steady state C_{maxss} and steady state trough plasma concentration (C_{minss}) using power model analysis.

Results

Following administration of 2, 4, 8, and 12 mg bd doses of Ilo, the ILO AUC_T increased 2.2, 4.4, and 7.7 fold, with the 2, 4, 6 fold increase in dose. The ILO C_{maxss} increased similarly. Thus, from 2 -8 mg/day bd ILO shows dose proportionality, with some slight deviation from dose proportionality at 12 mg bd.

Both P88 and P95 showed dose proportionality for doses between 2 – 12 mg bd: for P88, the AUC and C_{maxss} values showed 2.1, 4.3, and 6.5 fold increases; and for P97 the AUC and C_{maxss} showed 2.1, 4.3 and 6.4 fold increases at 2, 4, 8, and 12 mg bd, respectively.

While in the statistical model, the exponents were statistically significantly greater than 1 for AUC_τ, C_{maxss}, and C_{minss}, the difference from 1 was small and the 90% confidence interval limits were within the set boundaries of 0.68 and 1.32 to meet the dose proportionality criterion (90% confidence intervals (CIs) 1.06-1.17, 1.06-1.24, 1.10-1.21, for AUC_τ, C_{maxss}, and C_{minss}, respectively).

Pharmacokinetics in target population

The average plasma concentration (C_{avg}) at steady state at different doses for patients with schizophrenia was available from Studies 0211, 2001, 3005. The range of values by dose is described in Table 5.

Table 5. C_{avg} x dose

ILO Dose	C_{avg}^{ss}
12 mg/d	5.4 – 19.33
16 mg/d	6.99 – 12.35
20 mg/d	10.05
24 mg/d	11.79 – 20.88

Comparisons in PK between healthy volunteers and target populations, as maximum tolerability dose in healthy volunteers was 3 mg/day which is well below the doses used in target population studies, with the exception of Study 0112 which had 2 and 4 mg/day

doses. It is also well below the 12-24 mg/day range which is the recommended therapeutic dose range.

Special populations

Age

There have been no studies in elderly patients or children and adolescents. In Studies ILP2001 and VP-VYY-683-3101-PK01 no correlations of age and PK characteristics were observed.

Gender

The half-life of ILO or metabolites P88 and P95 did not vary with gender. However exposure (plasma concentration) is 48.4% larger in women than in men after adjustment for weight. The significance of this is not clear as there were no clinically significant differences in safety or efficacy observed by gender (see below).

Body Size

Body Mass Index (BMI) does no correlate with exposure (3101, 2001). However, a 2 fold increase in body weight yields a 15% increase in systemic pharmacokinetic parameters (clearances and volumes of distribution), of ILO and P88 and P95 which is equivalent to a 13% decrease in average exposure (3101).

Genotype

As described above, patients identified by genotype as poor CYP2D6 metabolisers have increased exposure to ILO and its main metabolites.

Renal Impairment

Study ILO 522 0102 evaluated the pharmacokinetics of ILO and metabolites P88 and P95 following a single 3 mg dose in individuals with severe renal failure on hemodialysis compared to healthy volunteers matched on gender, age, height, body weight and smoking status. Twenty-three subjects completed the trial.

There was little difference between the impaired group and healthy volunteers in C_{max} for ILO and its metabolites. For Ilo, renal impairment increased the mean AUC_T by 24% and $AUC_{0-\infty}$ was 80% higher (a difference driven largely by a single outlier in the renal group, excluding that patient $AUC_{0-\infty}$ for the two groups differed by 20%). Apparent clearance of ILO was 19% lower in subjects with renal failure compared to healthy controls. Half-life values were greater in subjects with renal impairment compared to healthy subjects (33.7 versus 15.0 h, respectively).

For P88, AUC_T decreased slightly (by 6%), while $AUC_{0-\infty}$ was 28% lower in subjects with renal impairment. For P95, mean $AUC_{0-\tau}$ was 52% higher in subjects with renal impairment whereas the mean $AUC_{0-\infty}$ was 217% higher. In subjects with renal failure, P95 concentrations did not decrease markedly between t_{max} and the end of the 63 h sampling period. This increase in $AUC_{0-\infty}$ for P95 in subjects with renal failure is to be expected given that P95 is the most abundant metabolite in urine in healthy subjects and renal elimination is the main elimination pathway for P95.

Severe renal failure decreased apparent ILO clearance by ~ 19%, corresponding to a 23% increase in exposure. The sponsor concluded that this was a small increase given variability in exposure in overall population.

The sponsor recommended dose adjustments for patients with renal impairment based on overall clinical evaluation.

Hepatic Impairment

Study ILO 522 0103 examined the effect of mild to moderate hepatic impairment (defined as mild; a Child-Pugh[6] score of 5 to 6 and moderate; a Child-Pugh score of 7 to 9) on the PK of Ilo, P88 and P95. Additionally subjects in the hepatic impaired group were required to have biopsy-proven hepatic cirrhosis and physical signs consistent with a clinical diagnosis of liver cirrhosis. Sixteen patients (4 mild, 4 moderate, 8 healthy) entered the study. A single 2 mg dose of ILO was used.

The apparent oral clearance and apparent volume of distribution of ILO in hepatic impaired subjects were 9.8% and 17% lower respectively, however, the exposure to ILO was essentially the same as in healthy subjects. Maximum plasma concentration and overall exposure to P88 were significantly higher, 71% and 50%, although there was no alteration in renal clearance. As P88 is active, exposure to combined active entities (ILO + P88) is approximately 30% higher in hepatically impaired subjects. For P95, C_{max} and AUC_T were slightly lower (19% and 20%) in impaired subjects with no change in renal clearance. Plasma protein-binding was not different between the impaired and healthy group. The sponsor recommended that dose adjustment due to hepatic impairment be based on overall clinical evaluation.

Evaluator's overall comments on pharmacokinetics in special populations

PK has been adequately assessed in extensive and poor CYP2D6 metabolisers in both patient and healthy volunteer cohorts, and in individuals with hepatic and renal impairment. There is no data on children adolescents or the elderly.

The draft PI provides a sufficient overview of PK parameters and indicated, based on PK findings, the circumstances in which adjustments may be required in dosing.

Interactions

In vitro studies tested the effects of ILO, P88 and P95 on various CYP450 isoenzymes. There was evidence of both direct and time-dependent inhibition of CYP2D6 and CYP3A4/5 by parent ILO and P88 but no indication of inhibitory activity for P95.

Three studies examined the effect of known CYP450 inhibitors substrates (0104, 0107 and 0108).

Study ILO 0104 examined potential interaction in healthy volunteers genotyped as extensive metabolisers using dextromethorphan hydrobromide (DEX), a CYP2D6 substrate. PK for both drugs and their metabolites were essentially unchanged by co-administration (that is, the AUC for ILO varied less than 5% when administered alone or in combination with DEX, and the AUC for DEX varied by less than 6% with and without ILO administration).

Study ILO 0108 examined the effect of Fluoxetine (20 mg), both a substrate and an inhibitor of CYP2D6 and also likely a CYP3A4 inhibitor, in healthy volunteer extensive metabolisers.

Exposure to ILO (at 3 mg) and P88 was significantly increased with concomitant administration of fluoxetine: $AUC_{0-\infty}$ showed a 131% and 119% increase and C_{max} showed a 70% and 64% increase for ILO and P88, respectively, compared to ILO alone. P95 was significantly decreased (53% for AUC and 70% for C_{max}). ILO did not alter the PK or metabolism of fluoxetine and norfluoxetine.

[6] The Child-Pugh score is used to assess the prognosis of chronic liver disease. The score employs five clinical measures of liver disease. Each measure is scored 1-3, with 3 indicating most severe derangement.

Study ILO 0107 examined the effect of concomitant administration of ketoconazole (KET at 200 mg), a CYP3A4 inhibitor, and ILO (3 mg) in healthy volunteers. Co-administration of KET increased exposure to ILO by approximately 50% ($AUC_{0-\infty}$ up 53% and C_{max} up 46%), and consequently increased exposure to metabolites P88 and P95 by 50 and 38%, respectively.

However, the degree of ILO protein binding and the fraction of the dose excreted in urine as the two metabolites were not affected by concomitant administration of KET.

Evaluator's Overall comments on PK Interactions

The three interaction studies examine potential effects of ILO on CYP2D6 substrates, and the effect of CYP2D6 and CYP3A4 on exposure to ILO, P88 and P95. There appears to be no interaction with CYP2D6 substrates, however both CYP2D6 and CYP3A4 inhibitors interact to increase the exposure to ILO and its metabolites. For CYP2D6, exposure to potent inhibitor fluoxetine doubled exposure to the two active compounds, ILO and P88. This indicates that co-administration of fluoxetine, or other CYP2D6 inhibitors, should be undertaken with caution, and dose reduction of ILO should be considered based on clinical assessment. Likewise, co-administration of ILO and KET, or other potent CYP3A4 inhibitors, substantially increases exposure to ILO and P88, and thus also requires caution and attention to dosage.

Based on PK data, the draft PI recommends the dose be halved when ILO is to be co-administered with fluoxetine, paroxetine, ketoconazole or other agents that inhibit the CYP2D6 or CYP3A4 metabolic pathways.

Exposure relevant for safety evaluation

Dose being recommended in target population is in the range of 12 mg/day to 24 mg/day per day.

Exposure at steady state at these dose levels, in the target population are given above.

Evaluator’s overall conclusions on pharmacokinetics

The pharmacokinetic development program was comprehensive, well conducted and the pharmacokinetic properties of the parent compound and two major metabolites are well characterised. Effects of CYP2D6 and CYP3A4 inhibition, and renal and hepatic impairment, have been well characterised, as has the effect on pharmacokinetic parameters in individuals who are poor CYP2D6 metabolisers.

The sponsor’s Clinical Overview was representative of the data.

Direct comparisons between PK parameters in healthy volunteers and patients are not available, as the maximum tolerable dose of 3 mg/day in healthy volunteers is lower than the majority of doses used in PK studies in target populations, and is also lower than dose level sought in the application (12-24 mg/day).

Pharmacodynamics

Introduction

Three Phase III clinical trials (3000, 3005, and 3101) examined pharmacodynamic characteristics of ILO and its main metabolites. One study was in a schizophrenia population only whilst two studies were in mixed schizophrenia and schizoaffective populations.

Relationship between plasma concentration and effect

The three pharmacodynamic studies in patients with schizophrenia examined doses from 4 mg/day – 24 mg/day, all of which were larger than the maximum tolerated dose in healthy volunteers (3 mg/day). The first study (3000) examined doses of 2 mg and 4 mg bd. That study found in PK/PD analysis a statistically significant correlation between the combined mean plasma concentration of ILO and metabolite P88 and a reduction of efficacy score in Positive and Negative Syndrome Scale – total score (PANSS-T), Positive and Negative Syndrome Scale – positive subscale (PANSS-P) and Positive and Negative Syndrome Scale – general psychopathology subscale, and Brief Psychiatric Rating Scale (BPRS). At plasma concentrations ≥5 ng/ml, a statistically significant greater proportion of ILO patients achieved a ≥20% reduction on the PANSS-T compared with those with plasma concentrations of ≤ 5 ng/ml.

Study 3005 examined doses of 6-8 mg bd and 10–12 mg bd. Multiple regression analysis found that change from baseline in PANSS-T, PANSS-P, PANSS-N, PANSS-GP and the BPRS were all significantly correlated with ILO mean concentration values. Unlike Study 3000, there was no statistically significant difference in ≥20% reduction between subjects with an ILO plasma concentration of ≥5 ng/ml or ≤5ng/ml plasma.

Study 3101 examined a 12 mg bd dose. That study found no statistically significant relationship between exposure metrics and change, or percentage change in efficacy for ILO and P88 at Weeks 2 or 4, although increasing AUC and C_{max} values were associated with larger improvement in efficacy scores. Increasing steady state AUC was associated with improved PANSS-T in analyses that included PBO subjects but not in those that did not include PBO subjects. There were indications that the relationship between exposure and change in efficacy measures plateaued at 30 ng/ml.

The two earlier studies do demonstrate a concentration efficacy relationship. In those studies the relationship between exposure and efficacy is demonstrated at lower levels of exposure and not at higher exposures (that is, at lower but not higher doses). These results suggest that lower doses in legacy studies were associated with a smaller magnitude of efficacy. The larger doses used in the early studies and the 24 mg/day dose in Study 3101 resulted in maximal efficacy after which no further increase in exposure increased efficacy.

Evaluator's overall conclusions on pharmacodynamics

PK/PD (exposure/response) relationships have been characterised across the dose range relevant to this application.

Efficacy

Introduction

Documentation was provided for seven safety and efficacy trials in support of the current Australian application. Conducted between 1998 and 2006 four are short term randomised, PBO- and active-controlled, double-blind, efficacy studies (3101, 3004, 3005, 3000), two of which have long term double-blind phases (3000, 3004) and three are long term double-blind studies (3001, 3002, 3003).

In consideration of the fact that the indication being sought is inconsistent with indications for all other currently available antipsychotic pharmacotherapies and that the submitted data should be considered with the EU guideline[1] which recommends not including schizoaffective patients in trials for schizophrenia, the evaluation of clinical efficacy takes as the primary efficacy outcomes the performance of the product in cohorts of patients with the diagnosis of schizophrenia. Three of the four short term double-blind,

PBO- and active-controlled studies (Studies 3000, 3004, 3005) include mixed schizophrenia and schizoaffective populations (ranging from 22% to 31% of the sample). Inclusion criteria for these three studies were a diagnosis of Diagnostic and Statistical Manual of Mental Disorders fourth revised edition (DSM-IV) Schizophrenia (code 295) with suffixes 10 – disorganized, 20 – catatonic, 30 –paranoid, 60- residual, 70 - schizoaffective, 90 – undifferentiated) and meeting Criterion A of DSM-IV schizophrenia criteria[7] for at least the 2 weeks prior to baseline.

Criterion A are also a requirement for a schizoaffective diagnosis, however while the indication sought specified schizophrenia, it did not seek an indication of schizoaffective disorder. Post hoc analyses can be undertaken to distinguish results in the Schizophrenia only subgroup of these studies, and were done so by the sponsor at the request of the FDA as part of the approval process in the USA. The following discussion of the submitted data and assessment of its adequacy will present the studies as designed (with mixed schizoaffective and schizophrenia populations) but will also focus on the outcomes in the schizophrenia only subgroups in those studies. The evaluator considered that it constitutes the key evidence that would support efficacy for the indication of schizophrenia.

Short-term efficacy

Of the four short term (4 – 6 week) double-blind, randomised, PBO and active controlled studies conducted for efficacy, two (3101 and 3004) demonstrate efficacy based on protocol defined outcomes in schizophrenia (3101) and schizophrenia and schizoaffective (3004) patients in the dose range proposed by the sponsor (12 – 24 mg/day). Two other placebo-controlled studies (3000 and 3005) although negative, they do provide some supporting evidence of efficacy for certain ILO doses. When assessing efficacy outcomes in schizophrenia only subgroups of the mixed population studies, one previously negative study (3005) becomes positive, the previously positive study (3004) becomes negative and Study 3000 remains negative.

Long-term efficacy

The long term double-blind phase of Studies 3000 and 3004 and Studies 3001, 3002 and 3003 provide data on long term efficacy outcomes up to 12 months.

Good Clinical Practice

All studies reviewed were designed and conducted in accordance with the Declaration of Helsinki and the relevant regulatory guidelines including the US Code of Federal regulation governing protection of human subject, Institutional Review Boards, and the

[7] Criterion A: **Characteristic symptoms**: Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated):

1. delusions
2. hallucinations
3. disorganized speech (for example, frequent derailment or incoherence)
4. grossly disorganized or catatonic behavior
5. negative symptoms, such as affective flattening, alogia, or avolition
   Note: Only one Criterion A symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person's behaviour or thoughts, or two or more voices conversing with each other.

obligations of clinical investigators, and with the International Conference on Harmonisation Guidance for Good Clinical Practice.

Dose response studies

With the exception of Study 3101 (24 mg/day only), the other three trials examined a range of doses of ILO. The first study conducted (3000) compared ILO 4, 8 and 12 mg/day, and while negative on protocol defined outcome (see below), secondary analyses found only the 12 mg/day separated from PBO on symptom scales (PANSS-T and BPRS). The next study (3004) included a higher dose level, 16 mg/day, and compared flexible dosing within predetermined ranges: 4-8 and 10-16 mg/day. It was positive on protocol defined outcomes and showed improvement over PBO in both dose groups, both dose ranges performing similarly. The final of these three studies (3005) also compared two flexible dose ranges and included a higher range 12-16 mg/day and 20-24 mg/day. This study was overall negative in protocol defined outcomes but secondary analysis showed superiority over PBO for the 20-24mg/day dose range. There was a sufficient range of doses with sufficient numbers. Dose selection for short term efficacy trials was initially based on evaluating a dose range (3000), and then expanding that range to determine efficacy at progressively higher doses. When examining dose in schizophrenia only groups, the higher dose range (20-24 mg/day) is supported by two studies (3101 and 3005) and the lower dose range (10-16 mg/day) by one (3005).

The pharmacokinetics of ILO, P88 and P95 are dose-proportional in the 2-12 mg bd. Deviation of ILO from dose-proportionality at 12 mg bd was small (1.5 fold increase in dose resulted in 1.75 fold increase in AUC_T), so for practical purposes can be considered to be dose proportional over the whole 2-24 mg/day range studied.

Data from clinical pharmacology studies in schizophrenia and schizoaffective patients indirectly suggests that dose may be expected to be related to efficacy. PK/PD modelling in the population PK/PD sub-study of 3101 indicated a relationship between plasma concentrations of ILO and efficacy (see above). Thus, given that there is a dose response in concentration (Study 0112) and a concentration related efficacy response (3101), it is expected that higher doses will be more efficacious. Across the four PBO-controlled studies in the schizophrenia only cohorts, findings are consistent with this, with no positive findings for the lowest doses studies 4-8 mg/day and positive findings for doses from 12-24 mg/day. Based on the above, the dose range proposed by the sponsor appears appropriate.

Specific dose related efficacy results will be reported in the relevant sections below.

Main studies

Study 3101 is clearly a pivotal study for the purposes of this application as it was conducted in a schizophrenia only sample and is positive on protocol defined outcomes. In selecting other pivotal studies in the light of the introductory discussion of the proposed indication (see *Introduction* above), pivotal studies were identified based on demonstrating efficacy in schizophrenia only samples. Thus, Study 3005 becomes the second pivotal study. Study 3004, while overall negative in the schizophrenia only subsample, is presented in some detail also as it was positive in protocol defined outcome in the original mixed population. Note that in these latter studies data was not available to describe the schizophrenia only population in terms of baseline demographics, loss to follow-up and so on. Thus, with the exception of efficacy outcomes all data given below is for the entire mixed schizophrenia and schizoaffective sample.

VP-VYV-683-3101

A randomised, double-blind, placebo and ziprasidone (ZIP) controlled, multicentre study to evaluate the efficacy, safety and tolerability of a 24 mg/day dose of ILO given bd for 28 days to patients with schizophrenia in acute exacerbation followed by a long term treatment phase.

Primary Objective

To evaluate the efficacy of a 24mg/day ILO dose compared to placebo over 28 days.

Step-down primary objective

To evaluate the efficacy of ILO compared to placebo in patients lacking the CNTF FS63Ter polymorphism (CNTF-). In the original study protocol this was a primary outcome, however the protocol was amended to make it a Step-down primary outcome to be tested only if the primary efficacy analysis was significant.

Secondary Objectives:

1. To evaluate the efficacy of ILO in patients with and without the CNTF FS63Ter polymorphism.
2. To evaluate the efficacy, tolerability and safety of ILO and ziprasidone compared with placebo.

Inclusion Criteria

· Males, non-fecund females or females using adequate contraception

· 18-65 years old, and over 65 years old on case by case basis

· BMI >18 and <35 kg/m2, BMI>35 kg/m2 considered case by case

· No medical contraindication for ILO treatment. DSM-IV schizophrenia (code 295) with suffixes 10 – disorganized, 30 –paranoid, or 90 – undifferentiated

· Baseline CGI-S[8] of at least 4

· Screening and baseline rating of at least 4 (moderate) on 2 of 4 PANSS positive symptoms: delusions, conceptual disorganization, hallucinatory behaviour, and suspiciousness/persecution

Exclusion Criteria

· DSM-IV schizophreniform and schizoaffective disorder

· Any other primary Axis I diagnosis or any axis to interfere with compliance

[8] The Clinical Global Impression - Severity scale (CGI-S) is a 7-point scale that requires the clinician to rate the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis. Considering total clinical experience, a patient is assessed on severity of mental illness at the time of rating 1, normal, not at all ill; 2, borderline mentally ill; 3, mildly ill; 4, moderately ill; 5, markedly ill; 6, severely ill; or 7, extremely ill.

- Diagnosis or history of DSM-IV chemical dependence, or toxic psychosis in prior 6 months, or clinical presentation possibly confounded by use of recreational drugs or alcohol
- Hospitalised more than 14 days immediately prior to screening
- Mentally disabled, brain trauma or coma lasting more than 24 hours
- At imminent risk of harm to self or others
- Positive test for amphetamines, cocaine, phencyclidine (PCP) or opiates
- Significant physical illness in 4 weeks prior to baseline
- Recurring clinically significant medical conditions
- Known congenital long QT syndrome
- Clinically significant disease or functional abnormality of gastrointestinal system, liver or kidneys
- Abnormal laboratory results
- Other medical conditions that would put patient at special risk or bias the assessment of clinical and mental status of patient to a significant degree
- Received experimental drug in 30 days prior to screening, or a drug known to cause major organ system toxicity or mood stabilizers in 30 days prior to baseline, or prior treatment with clozapine
- Electroconvulsive therapy (ECT) 3 months prior to baseline
- Likely to need continuous treatment with other psychotropics including antidepressants or mood stabilizers, during the entire study duration.
- Experienced neuroleptic malignant syndrome
- Had psychotic symptoms that failed to improve following sufficient exposure to therapeutic dose of any antipsychotic treatment over the last 2 years

Treatments

Study treatment doses: 24mg/day ILO and 160 mg/day ZIP.

The choice of ILO dose was based on data from an earlier trial (3005) indicating the dose was safe and well tolerated. The ZIP dose was chosen in accordance with its product label information.

Primary efficacy outcome

Change from baseline to last scheduled observation in the PANSS-T score.

Secondary efficacy outcomes

Change from baseline to last scheduled observation in the following scales; BRPS, PANSS-P, PANSS-N, ANSS-GP CDSS, CGI-C and CGI-S.

Sample size

Sample size calculation was based on PANSS-derived BPRS change from baseline at endpoint where the standard deviation (SD)=11.9 for ILO, 12.6 for PBO, and 12.0 for ZIP. ILO and PBO SDs based on data from an earlier trial (3005) and the SD for ZIP based on the literature.

Based on a t-test, to detect a 4 point change in PANSS derived BPRS between ILO and PBO a sample of 300 ILO patients and 150 PBO patients was needed to have 90% power with a two-sided α=0.05.

For subgroup analysis, in a group of 300 receiving Ilo, it was that assumed approximately 210 are CNTF- and 90 CNTF+; this would provide 60% power with α=0.05 to detect 4 point change in PANSS derived BPRS between genotype groups.

A sample size of 150 in the ZIP group provides 80% power with α=0.05 to detect 4 point change in PANSS derived BPRS between ZIP and PBO.

Randomisation

Each participant received subject identification (ID) comprising a 3 digit site number (site numbers assigned by Vanda) and a 4 digit patient number sequentially assigned by interactive voice response system (IVRS) at time of screening. Each subjects ID number was assigned by the site investigator calling IVRS during screening for the next available patient number.

A computer generated randomisation schedule was prepared prior to the start of study. Randomisation was centralised by country and utilised randomisation blocks consisting of 4 ILO treatment groups, 2 ZIP treatment groups and 2 PBO groups.

Blinding

This was a double-blind trial. The sponsor, investigators and their staff, statistical analysis/laboratory personnel and subjects were unaware if subject received an active or placebo treatment.

Statistical methods

Primary Outcome. A mixed model repeated measure model (MMRM). Analyses were adjusted for heterogeneity at baseline and heterogeneity among centres. MMRM used observed case (OC) dataset for all scheduled visits and if unscheduled visit or early termination occurred subsequent to scheduled assessments, then this value was carried forward to the missing next scheduled visit (but did not carry beyond that next scheduled visit to the end of the study).

Additional analyses. Additional MMRM analyses with baseline and outcome and re-randomisation approach for data normalisation were conducted for the primary outcome variable. There were no adjustments for multiplicity for these analyses and as they both yielded similar results to the baseline-as-covariate model, all further analyses used that model only.

Results from the MMRM analyses were declared a priori as primary. As MMRM was conducted using an OC dataset and under the assumption that values are missing at random, an analysis of co-variance (ANCOVA) were conducted on last observation carried forward (LOCF) imputed data and OC data as sensitivity analyses of assumptions about missing values, for primary outcome measure and secondary efficacy variables and subgroup analyses.

Analyses of efficacy in subgroups (CTNF- versus CTNF+ in ILO patients, ZIP versus PBO) were conducted as above (MMRM and ANCOVA for sensitivity) and analyses of secondary efficacy variables was conducted as described above for primary outcome analysis and sensitivity analysis.

Population. All efficacy analyses where conducted based on a Modified Intent to Treat (ITT) Population. The modified ITT population included all randomised patients who received at least one dose of study medication and from whom a baseline PANSS score was obtained and at least one post-baseline PANSS efficacy measurement was obtained while on study medication. Patients randomised in error were excluded from the modified ITT population.

Adjustment for multiplicity. Sample size was calculated for the Primary and Step-down primary analysis. On this basis no further adjustment was deemed necessary for multiplicity in the primary analysis to protect the overall experimental error rate of 0.05. There was no adjustment for multiplicity in analyses of secondary parameters.

Results

Some 606 of the 913 screened patients were assigned to randomisation and 593 were randomised to the study: 295 to ILO 24 mg/day, 151 to ZIP and 152 to PBO. Some 212 (35.8%) subjects discontinued during Days 1-28: 102 (34.6%) given ILO 24 mg/day, 51 (34.2%) given ZIP and 59 (39.6%) given PBO. Table 6 gives reasons for discontinuation.

Table. 6 Reasons for discontinuation

	ILO 24 mg/d N=295	**ZIP 160mg/d N=149**	**PBO N-149**	**Total N=593**
Primary reason				
Adverse event	16 (15.7%)	13 (25.5%)	11 (18.6%)	40 (18.9%)
Unsatisfactory therapeutic effect	21 (20.6%)	12 (23.5%)	19 (32.2%)	52 (24.5%)
Protocol deviation	2 (2.0%)	1 (2.0%)	1 (1.7%)	4 (1.9%)
Withdrawal of Consent	59 (57.8%)	23 (45.1%)	21 (35.6%)	103 (48.6%)
Lost to Follow-up	0	0	2 (3.4%)	2 (0.9%)
Other	4 (3.9%)	2 (3.9%)	5 (8.5%)	11 (5.2%)
Total Discontinued	102 (34.6%)	51 (34.2%)	59 (39.6%)	212 (35.8%)
Completed day 42	193 (65.4%)	98 (65.8%)	90 (60.4%)	381 (64.2%)

Recruitment

The first patient was recruited on 18 November 2005 and the last patient completed the study on 26 September 2006.

Protocol amendments

There were no major amendments to the protocol. Minor amendments include the limiting of sites to the USA and India (not including as previously planned Mexico, Canada and Singapore) and reclassifying the second primary objective as a Step-down primary objective.

Protocol compliance and CGP inspection findings

Full records were provided regarding dosage and compliance for each patient. Eleven of the 44 sites were audited, with signed audit completion forms included. There was no information provided regarding content of audit reports or any inspection on other sites. Study-approved deviations in protocol were recorded in the patient study documentation but have not been provided here.

Baseline data

Table 7 shows baseline demographic and clinical characteristics of the Ilo, ZIP and PBO Groups.

Table 7. Baseline demographic and clinical characteristics.

	ILO	ZIP	PBO
Demographics			
Age (mean, SD, range)	39.5 ±10.4 (18-65)	40.0 ±9.9 (20-15)	40.7 ±10.4 (19-64)
Sex (%male)	83.1%	75.8%	76.5%
Race (%)			
Black	49.8%	51.0%	51.0%
White	37.6%	34.2%	30.9%
Asian	8.5%	8.1%	10.1%
DSM IV Diagnosis			
Schizophrenia - Disorganized	4.4%	2.0%	4.7%
Schizophrenia - Paranoid	83.4%	85.2%	85.9%
Schizophrenia - Undifferentiated	12.2%	12.8%	9.4%
Baseline Clinical measures			
PANSS-T	92.67±13.06	90.95±11.46	90.32±11.19
PANSS-P	24.91±3.83	23.97±3.68	23.52±3.71
PANSS-N	22.45±4.43	22.88±4.69	22.33±4.49
PANSS-GP	43.31±7.80	44.09±6.50	44.48±6.70
BPRS	54.50±8.03	53.26±6.69	52.72±6.91
CGI-S	4.71±0.62	4.67±0.63	4.59±0.64
CDSS	4.01±3.80	3.70±3.46	3.88±3.32

The only statistically significant difference between the three groups was the PANSS-P score. The PANSS-P score was statistically significantly higher in the than ILO group than the PBO group.

The study population is an appropriate reflection of the intended target patient population.

Compliance

This was an inpatient study and so had high treatment compliance. Based on the ratio of adherence to schedule versus patients remaining in the study overall compliance was 99-100%.

Numbers analysed

There were two analytical datasets: The modified ITT dataset, which was used in LOCF analyses, comprised 283/300, 144/150, 140/147 of subjects who received allocated treatment with Ilo, ZIP and PBO, respectively.

The Observed Cases in the modified ITT population dataset described above and used in MMRM analyses and ANCOVA of OC sensitivity analyses. At study defined endpoint Day 28, that dataset comprised 200/283**,** 102/150, 92/140 subjects in the Ilo, ZIP and PBO groups, respectively.

Numbers for genotype sub-analyses are presented in the results sections.

Outcomes and estimation. Entire Study Population (Schizophrenia and Schizoaffective Disorder mixed)

Primary outcome. MMRM analysis resulted in a significant difference between ILO and PBO in change in PANSS-T score at study endpoint (28 days or last scheduled visit), with an average 4 point greater improvement for the ILO group than the placebo group.

Table 8 below gives outcomes and estimates for the protocol defined primary outcome efficacy variable change in PANSS-T score at study endpoint (28 days or last scheduled visit). MMRM analysis was the primary analysis, with the ANCOVA for LOCF and observed cases conducted as a sensitivity analysis.

The MMRM and LOCF ANCOVA analysis showed a statistically significant difference between ILO and PBO groups in mean change in PANSS-T scores from baseline to Day 28 whereas the OC analysis did not.

Table 8. Change in PANSS-T score at study endpoint (28 days or last scheduled visit)

Analysis	ILO (n= 283) adjusted change (SE)	PBO (n=140) adjusted change (SE)	ZIP* (n=150) adjusted change (SE)	Mean difference ILO & PBO (SE)	P value, 95% CI ILO vs. PBO
MMRM	-12.01 (1.03)	-7.08 (1.48)	-12.27±1.44	-4.92 (1.80)	P=0.006; 95% CI-8.47, -1.14
ANCOVA (LOCF)	-11.03±15.68	-6.85±17.57		-4.20 (1.69)	p =0.013 95%CI= -7.53;-0.87
ANCOVA (OC)	-14.59(.99)	-12.84(1.49)		-1.75 (1.81)	p=0.334 95%CI-5.32,1.81

Adj. change = least squared mean change from the ANCOVA model.
*included for descriptive purposes only

A Cohen's d calculation[9] for the effect size comparing ILO versus PBO was .251023, indicating a small effect (http://www.danielsoper.com/statcalc/calc48.aspx). This was the same for ZIP.

Secondary efficacy variables. In analysis on continuous secondary efficacy variables ILO showed a significantly greater reduction in mean scores from baseline to study endpoint on BPRS, PANSS-P, and CGI-S in MMRM analysis and LOCF ANCOVA analysis. CDSS, PANSS-N and PANSS-GP did not differ between PBO and ILO in mean change from baseline to study endpoint. Table 9 gives point estimates and 95% CIs.

[9] Cohen's d=(two-tailed) effect size for a Student t-test.

Table 9. MMMR, LOC, OC analyses: mean difference between ILO and PBO groups in secondary efficacy variable score change from baseline to study endpoint (28 days or last scheduled visit)

	MMRM Mean (SE), p (95%CI) N= 200 ILO N= 90 PBO	LOCF Mean (SE), p (95%CI) N=383 ILO N=140 PBO	OC Mean (SE), p (95%CI) N= 200 ILO N= 90 PBO
PANSS-P	-1.99 (0.60) p<0.001 (-3.17,-0.82) (ZIP -4.23 SE 0.38)	-1.68 (0.56) p=0.003 (-2.87,-0.57)	NS
PANSS-N	- 1.05 (0.48) p=0.27 (-1.98,-0.11) (ZIP -3.06 SE 0.38)	-1.00 (0.45) p=0.027 (-1.88,-0.12)	NS
PANSS-GP	NS	NS	NS
BPRS	-2.77 (1.11) p=0.013 (-5. 08,-0.09) (ZIP -7.21 SE 0.89)	-2.30 (1.05) p=0.029 (-4.87,-0.24)	NS
CGI-S	-0.26 (0.10) p=0.007 (-0.45,-0.07) (ZIP 0.67 SE 0.08)	-0.25 (0.09) p=0.007 (-0.43,-0.07)	NS
CDSS	NS	NS	NS

CGI-C Categorical analysis conducted on LOCF dataset. At Day 28 a significantly greater proportion of the ILO group (183/283, 64.7%) compared to the PBO group (73/140, 52.1%) had experienced some improvement (difference 12.52%, p=0.041, 95% CI 2.55-22.50). There was no difference in proportion improved in the OC dataset.

A further set of analyses compared the proportion in the ILO and PBO groups who experienced a 20% reduction in scores from baseline to study endpoint on all continuous efficacy scales. A statistically significant greater proportion of the ILO group achieved a 20% reduction compared to the PBO group in PANSS-T, BPRS, PANSS-P scores but not PANSS-N, CGI-S, CDSS, PANSS-GP.

Efficacy in ILO (CNTF-) compared to PBO (CNTF-)

There was a statistically significant difference between ILO CNTF- and PBO CNTF- groups in mean score change from baseline to Day 28 (or last scheduled visit) in MMRM analysis (ILO -12.05 (standard error (SE) 1.17) versus PBO -5.68 (SE 1.69); mean difference -6.37 (SE 2.05), p=0.002 95% CI -10.39,-2.84). LOCF sensitivity analysis found virtually the same results and the OC analysis was not significant. Note that the effect size for ILO was more or less the same as in the entire sample but the PBO group had a poorer outcome leading to a somewhat overall greater mean difference between the two groups in this sub-sample.

In analyses of secondary efficacy variables in the CTNF- subgroups for the PANSS-P, PANSS-N, PANSS-GP, BPRS and CGI-S there was a statistically significant difference between ILO CNTR- and PBO CNTR- groups in mean score change from baseline to Day 28 (or last scheduled visit) in MMRM analysis and in LOCF analysis. Only the PANSS-P was also statistically significant in the OC analysis. There were no group differences on the CDSS.

In LOCF categorical analysis, at Day 28 there was a significantly greater proportion of ILO CNTF- group with improvement compared to PBO CNTF- (ILO 140/218 64.2% versus PBO 53/107 49.5%; mean difference 14.7%, p=0.014, 95% CI 2.28,26.10). There was no significant difference in the OC analysis.

Efficacy in ILO (CNTF-) compared to ILO (CNTF+)

There were no differences in score changes between ILO- and ILO+ on any scale administered.

Group sizes were as follows for the LOCF dataset; ILO CNTF- 218 subjects and ILO CNTF+ 61 subjects. It is unlikely the study was appropriately powered to detect differences between these groups.

Efficacy, safety and tolerability of ILO and ZIP compared to PBO

ZIP was included as an active control to validate the study and the study was not designed as a head-to-head comparison of ILO and ZIP. Results for ZIP are included in tables above.

In MMRM the decrease in scores from baseline to study endpoint (Day 28 or last scheduled visit) was statistically significantly greater for the ZIP group than the PBO group for PANSS-T (-12.27 SE1.44, p<0.05), PANSS-N (-3.06 SE 0.38, p=0.036), PANSS-P (-4.23 SE 0.48, p=0.003), BPRS (-7.21 SE0.89, p=0.042) and CGI-S (-0.67 SE 0.08, p=0.013). There was no difference for the PANSS-GP and the CDSS. LOCF analysis also found a statistically significant difference between groups for these variables while OC did not. In LOCF categorical analysis there was no difference in improvement between ZIP and PBO in CGI-G at study endpoint (Day 28) but there was significant improvement at Day 14 and Day 21 (p=0.005 and p=0.002 respectively).

Study ILP3005

A randomised, double-blind, placebo and risperidone controlled, multicentre study to evaluate the efficacy and safety of two non-overlapping does ranges of ILO given bd for 42 days to patients with schizophrenia, followed by a long term treatment phase with ILO given once a day (qd).

Note: The evaluators suggested that this study be accepted as a pivotal study providing evidence of efficacy for ILO in schizophrenia based on post hoc analysis of the schizophrenia-only sub-sample. Except where indicated the following describes the entire study population (schizophrenia and schizoaffective disorder patients mixed). Efficacy results from post hoc analysis of the schizophrenia only subgroup are presented at the end of the section.

Methods

Primary Objective. To evaluate the efficacy and safety ILO 12-16 mg/day and 20-24 mg/day and risperidone (RIS) 6-8 mg/day compared with placebo over 42 days in patients with schizophrenia or schizoaffective disorder.

Secondary objectives. Protocol amendment added the secondary objective: "To demonstrate the effect of ILO on negative symptoms of schizophrenia over 42 days."

Similar to amendments to Study 3004, additional evaluations at certain sites were added in protocol amendments including neurocognitive function, quality of life, resource utilization and functionality assessments, pharmacogenetic and positron emission tomography (PET). These are not discussed here as they are small scale and exploratory.

Study Participants. Inclusion and Exclusion Criteria were similar to Study 3101.

Treatments. Study treatment doses: 12 or 16 mg/day Ilo, 20 or 24 mg/day and 6 or 8 mg RIS.

Two non-overlapping doses ranges of ILO were used to explore treatment effects at these dosages. Flexible dosing was used to address individual differences between patients in response and tolerability and to reflect clinical practise. RIS was chosen as active reference therapy because of its well established efficacy and tolerability. The RIS dose levels were as advised in package insert.

Primary efficacy outcome: Change from baseline to endpoint (Day 42 or premature discontinuation) on the 18-item PANSS-derived BPRS.

Secondary efficacy outcomes:

- Change from baseline to endpoint on PANSS-T, PANSS-P, PANSS-N and PANSS-GP.
- Proportion of patients who achieved a 20% or greater reduction on BPRS, PANSS-T, PANSS-P, PANSS-N and PANSS-GP.
- Proportion rated as minimally, much, or very much improved on CGI-C at each time point.
- Mean change from baseline in CGI-S and Scale for the Assessment of Negative Symptoms (SANS) at each time point.
- Change from baseline to endpoint on the CDS scale and Scale to Assess Unawareness of Mental Disorder (SUMD).

Sample Size. Sample size calculation based on BPRS change from baseline at endpoint where the SD=12. SD was based on data from ILP3000, which compared ILO 12 mg/day to PBO. A sample size of 150 patients per arm allowed the detection of a approximately 4 point difference between ILO and PBO with 80% power and with a two-sided alpha=0.05.

Randomisation. Each screened patient assigned a patient number by Interactive Voice Response System (IVRS). Number included 3-digit site number and 4 digit patient number. Patient IDs remained the same through all phases of the study and were not reassigned if the patient discontinued. Randomisation performed using IVRS. A computerised randomisation schedule was generated.

Initial randomisation was 2:1:1 for ILO 12-16 mg/day, RIS, and PBO. When the ILO 20-24 mg arm was added following results of Study 3004 which indicated a potential benefit from higher dose of ILO, approximately when half the anticipated enrolment had been completed, patients were thereafter randomised in a ratio of 1:2:1:1 to ILO 12-16 mg/day, ILO 20-24 mg/day, RIS and PBO.

Blinding. This was a double-blind trial. The sponsor, investigators and their staff, and subject were unaware of if subject receiving an active or placebo treatment.

Statistical methods

Primary Outcome. Adjusted mean change from baseline to Week 6 endpoint on the BPRS analysed in the LOCF dataset using ANCOVA model including treatment, centre, and baseline BPRS and treatment-by-baseline BPRS.

To control for multiplicity in analysis of primary outcome (efficacy of ILO compared with PBO) the primary comparison was between the ILO 12-16 mg/day group and the PBO group. If this test was significant at the 0.05 level, the subsequent pairwise comparison of the ILO 20-24 mg/day group with PBO would be considered significant at the 0.05 level. If

the initial comparison was not significant, the Step-down comparison would not be considered significant regardless of the nominal significance level.

Population. All efficacy analyses are based on the ITT population. The ITT population included all randomised patients who received at least one dose of double-blind study medication during the initial double blind phase and from whom at least one efficacy measurement (complete PANSS assessment) was obtained during that phase. Some 671 patients met these criteria (230 given ILO 12-16 mg/day, 141 given ILO 20-24 mg/day, 148 given RIS and 152 given PBO) and constituted the LOCF dataset.

Secondary analyses conducted in an Observed Cases dataset will not be discussed here.

Adjustment for multiplicity. A Step-down approach was taken for the primary efficacy analysis to address multiplicity. No adjustments for multiplicity were carried out for secondary efficacy variables, or secondary outcome analyses.

Subgroup Analyses. Analyses of efficacy in subgroups (RIS versus PBO) were conducted as described above.

Secondary analysis of efficacy

Analyses of continuous secondary efficacy variables were conducted as described above. Categorical variables analysed using Cochran-Mantel-Haenszel test, blocking on centres.

Note: Post hoc reanalysis using MMRM was conducted for this study.

Results

Participant flow

Some 706 of 945 screened patients were randomised the study; 244 to ILO 12-16 mg/day, 145 to ILO 20-24 mg/day, 157 to RIS and 160 to PBO. Some 401 (58%) subjects discontinued during Days 1-42: 46% of ILO 12-16 mg/day, 41% of ILO 20-24 mg/day, 29% of RIS and 46% of PBO. Table 10 gives reasons for discontinuation.

Conduct of the study

Protocol amendments: There were several protocol amendments, most of which concerned adding additional secondary study outcomes, as described above.

Table 10. Reasons for discontinuation

	ILO 12-16mg/d (n=244)	ILO 20-24mg/d (n=145)	RIS 6-8mg/d (n=157)	PBO (n=160)	Total (n-706)
Primary reason					
Treatment Emergent Adverse Event	8 (3%)	7 (5%)	7 (4%)	4 (3%)	26 (4%)
Non-treatment emergent adverse event	1 (0%)	0 (0%)	1 (0%)	2 (%1)	4 (1%)
Unsatisfactory therapeutic effect	57 (23%)	33 (23%)	12 (8%)	46 (29%)	148 (21%)
Abnormal Lab Value	10 (0%)	0	1 (1%)	1 (1%)	3 (0%)
Abnormal Test Procedure	0			0	1 (0%)
Condition no longer requires study drug	1 (0%)	0	0	0	1 (0%)
Protocol Violation	4 (2%)	1 (1%)	3 (2%)	1 (1%)	9 (1%)
Withdrawal of consent	29 (12%)	12 (8%)	14 (9%)	12 (8%)	67 (9%)
Lost to Follow Up	9 (4%)	6 (4%)	7 (4%)	6 (4%)	28 (4%)
Administrative problem	3 (1%)	0	0	0	3 (0%)
Total Discontinued	113 (46%)	59 (41%)	45 (29%)	73 (46%)	290 (41%)
Completed day 42	127 (52%)	85 (59%)	111 (71%)	87 (54%)	410 (59%)

Protocol compliance and CGP inspection findings: Sponsors note the existence of a Good Clinical Practice (GCP) Quality Assurance Unit within the company that conducts audits of clinical research activities to evaluate compliance with the principles of GCP, however no information is provided regarding audits conducted or protocol compliance monitoring and performance in the conduct of this study.

Baseline Data

Table 11 shows baseline demographic and clinical characteristics of the ILO, RIS and PBO Group.

There were no significant differences between treatment groups indicating successful randomisation.

Compliance: Treatment compliance was assessed by investigator and measured by capsule use (based on returned capsules) and feedback from patient, caregiver and study staff. Treatment compliance ranged from 89-94% across all treatment groups. Some 6.9% of patients had dose interruptions.

Numbers analysed. Of 706 patients randomised, 671 patients received at least one dose of study medication and had one complete efficacy measure obtained (230 ILO 12-16 mg/day, 141 ILO 20-24 mg/day, 148 RIS and 152 PBO.) These constitute the LOCF dataset.

Table 11. Baseline demographics and clinical characteristics

	ILO 12-16mg/d	ILO 20-24 mg/d	RIS	PBO
Demographics				
Age (mean, SD, range)	38.9±11.0 (18-65)	37.3±10.7 (19-65)	39.8±10.4 (18-64)	390±10.3 (18-69)
Sex (%male)	60%	68%	61%	59%
Race (%)				
Black or Afro-American	28%	23%	17%	24%
White	67%	57%	76%	69%
Other	6%	7%	6%	7%
DSM IV Diagnosis				
Schizophrenia - Disorganized	7 (3%)	11 (8%)	5 (3%)	5 (3%)
Schizophrenia - Paranoid	162 (66%)	89 (61%)	106 (68%)	108 (68%)
Schizophrenia - Undifferentiated	19 (8%)	14 (10%)	15 (10%)	7 (4%)
Schizoaffective	56 (23%)	31 (21%)	31 (20%)	40 (25%)
Baseline Clinical measures				
BPRS	54.4±7.4	55.0±9.0	55.2±9.0	55.3±8.1
PANSS-T	93.7±13.2	94.8±15.9	95.8±16.3	94.9±15.2
PANSS-P	24.8±3.6	24.4±4.3	24.8±4.2	24.5±3.8
PANSS-N	23.4±5.3	23.8±6.4	24.2±6.3	23.8±6.1
PANSS-GP	45.5±7.5	46.6±8.1	46.9±8.8	46.5±8.4
CGI-S	4.3±1.6	4.5±1.4	4.5±1.4	4.4±1.5
CDSS	5.6±4.6	5.7±4.8	5.6±4.6	5.7±4.8
SANS	53.0±21.9	54.9±23.9	54.2±24.3	54.1±23.5

Outcomes and Estimation – Entire Study Population (Schizophrenia and Schizoaffective Disorder mixed)

Primary outcome

There was a numerically but not a statistically significantly greater reduction in mean BPRS scores in the ILO 12-16 mg/day group compared to PBO at study endpoint (Day 42). As the primary outcome was not statistically significant the results of the Step-down primary outcome could not be considered even though they did show a statistically significant reduction on the BPRS at study endpoint for the ILO 20-24 mg/day group compared to PBO. Table 12 gives point estimates and 95% confidence intervals. The RIS group showed a significant reduction compared to PBO at study endpoint.

Note: Post hoc reanalysis using MMRM finds slightly different results, confirming the difference in score reduction between the ILO 20-24 mg/day group and the PBO group (mean difference from PBO -3.84, 95% CI -6.91,-0.76, p=014) while the difference between the ILO 12-16 mg group and PBO group becomes significant (Mean change from PBO -2.77, 95% CI -5.54,0.01, p=0.05).

Secondary efficacy variables and analyses

There were significant differences between the 20-24 mg/day ILO dosage group and the PBO group, but not the ILO 12-16 mg/day group and the PBO group, in reduction in scores at study endpoint (Day 42) for the PANSS –T, PANSS-P, PANSS-N, PANSS-GP. Both ILO groups showed a statistically significant greater reduction than the PBO group in CGI-S scores. Table 12 provides details of comparisons between ILO groups and PBO on the primary and continuous secondary efficacy variables.

The proportion of patients with a ≥20% improvement at study endpoint in BPRS, PANSS-T, PANSS-N, PANSS-P, and PANSS-GP was significantly higher in the ILO 20-24 mg/day

group, but not the ILO 12-16 mg/day group, compared to PBO. A significantly greater proportion of patients in the ILO 20-24 mg/day group but not the ILO 12-16 mg/day group showed improvement in CGI-C compared to PBO (ILO 12-16 mg/day 57/229 (74%), ILO 20-24 mg/day 91/140 (65%) and PBO 76/152 (50%), p=0.235 and 0.033, respectively).

Risperidone versus PBO

- The RIS group has a statistically significant greater decrease in score on all efficacy variables (BPRS, PANSS-T, PANSS-P, PANSS-N, PANSS-GP, CGI-S) than the PBO group. For descriptive purposes only the RIS adjusted mean change from baseline scores on efficacy scales are in included in Table 12.
- The proportion of patients with a ≥20% improvement in BPRS, PANSS-T, PANSS-N, PANSS-GP and PANSS-P was significantly greater in the RIS group than the PBO group.
- CGI-C improvement: A significantly greater proportion of the RIS group showed improvement in CGI-C compared to the PBO group; PBO 76/152 (50%), RIS 114/148 (77%), p<0.001. 27- 17,37.

Efficacy in Schizophrenia only subgroup

In post hoc analysis of the schizophrenia subgroup (78% of the sample), the ILO 12-16 mg contrast with PBO was significant (least squares (LS) mean difference in BPRS scores between ILO and PBO in change from baseline to study endpoint being -3.1, 9(5% CI -5.9, -0.3, p=0.033) and the Step-down comparison of ILO 20-24 versus placebo was highly significant (LS mean -4.5, 95% CI -7.6, -1.3, p=0.005). RIS, the active comparator, was also superior to PBO in this group (LS mean -7.1, 95% CI -10.2, -4.0, p<0.001).

Table 12. Change in primary (BPRS) and secondary efficacy variables at study end (Day 42 or premature discontinuation) in ILO 12-16 mg/day, ILO 20-24 mg/day and PBO groups.

Analysis	ILO 12-16 mg/d (n= 153)	ILO 20-24 mg/d (n=149)	PBO (n=152)	ILO 12-16 vs. PBO LS mean, P value, 95% CI	ILO 20-24 vs. PBO LS mean, P value, 95% CI
	adjusted change	adjusted change			
BPRS*	7.1	8.6	5.0 (RIS# 11.5)	LS mean: 2.1 , P=0.09; 95% CI -0.3,4.5	LS mean: 3.5, P=0.01; 95% CI 0.9,6.2
PANSS-T	11.0	14.0	7.6 (RIS# 18.8)	LS mean:3.3 , P=0.10; 95% CI -0.6,7.3	LS mean: 6.4, P=0.005; 95% CI 1.9,10.8
PANSS-P	4.2	5.1	3.1 (RIS# 7.2)	LS mean:1.0 , P=0.11; 95% CI -0.2,2.3	LS mean: 1.9, P=0.008; 95% CI 0.5,3.4
PANSS=N	2.2	2.8	1.5 (RIS# 3.5)	LS mean:0.7 , P=0.185; 95% CI -0.3,1.7	LS mean: 1.3, P=0.023; 95% CI 0.8,3.1
PANSS-GP	4.7	5.9	2.8 (RIS# 7.9)	LS mean:1.9 , P=0.07; 95% CI -0.2,3.9	LS mean: 3.1, P=0.007; 95% CI 0.8,5.4
CGI-S	0.6	0.6	0.4 (RIS# 0.9)	LS mean:0.2 , P=0.028; 95% CI 0.0,0.5	LS mean:0.2 , P=0.037; 95% CI 0.0,0.5

Adjusted change = least squared men change from the ANCOVA model (including treatment, centre, baseline and the treatment-by-baseline)
* Change is calculated as pre-post baseline value so that a positive change indicates improvement.
# Risperidone values have been given for comparison only.

Study ILP3004

A randomised, double-blind, placebo- and risperidone- controlled, multicentre study to evaluate the efficacy and safety of two non-overlapping does ranges of ILO given bd for 42 days to patients with acute or subacute exacerbation of schizophrenia, followed by a risperidone-controlled, long term treatment phase with ILO given qd.

Note: This study was positive based on the original protocol specified outcomes and study sample, however post hoc analysis of efficacy in the schizophrenia only sub-sample was negative. The evaluator did therefore not consider that this study provides evidence of efficacy for ILO in schizophrenia. As above, except when indicated, all the following described the entire study population (schizophrenia and schizoaffective disorder patients mixed). Data from post hoc analysis of the schizophrenia only subgroup will be indicated below.

Methods

Primary Objective. To evaluate the efficacy and safety of two non-overlapping dose ranges of ILO 4-8 mg/day (administered as 2-4 bd) and 10-16 mg/day [administered as 5-8 mg bd] and risperidone (4-8 mg/day administered as 2-4 mg bd) compared with placebo, over 42 days in patients with an acute or subacute exacerbation of schizophrenia or schizoaffective disorder.

Study Participants. Inclusion and Exclusion criteria are comparable to 3101 and 3005. This was a multi-centre study.

Treatments. Study treatment doses: 4-8 mg Ilo, 10-16 mg ILO and 4-8 mg RIS.

Two non-overlapping doses ranges of ILO were used to explore treatment effects at these dosages. Flexible dosing was used to address individual differences between patients in response and tolerability and to reflect clinical practise. RIS chosen as active reference therapy because of its well established efficacy and tolerability. The RIS dose levels used were as per package insert.

Primary efficacy outcome.

- Change from baseline to endpoint (Day 42 or premature discontinuation) on the 18-item PANSS-derived BPRS.

Note: Primary efficacy variable was revised from the PANSS-T to the PANSS-derived BPRS as results from Study ILP3000 indicated that the BPRS might be more sensitive in assessing treatment effects.

Secondary efficacy outcomes

- Change from baseline to endpoint on PANSS-T, PANSS-P, PANSS-N, and PANSS-GP.
- Proportion of patients who achieved a 20% or greater reduction on BPRS, PANSS-T, PANSS-P, PANSS-N, PANSS-GP
- Proportion rated as minimally, much, or very much improved on CGI-C at each time point
- Mean change from baseline in CGI-S at each time point.

Sample Size. The sample size calculation was based on PANSS-derived BPRS change from baseline at endpoint where the SD=12. SD based on data from Study ILP3000, which compared ILO 12 mg/day to PBO. A sample size of 150 patients per arm allowed the detection of a approximately 4 point difference between ILO and PBO with 80% power and with a two-sided alpha=0.05.

Randomisation and Blinding. Randomisation was performed using the same IVRS protocol as Studies 3101 and 3005.

This was a double-blind trial. The sponsor, investigators and their staff, and subject were unaware of if subject receiving an active or placebo treatment.

Statistical Methods

Primary Outcome. To control for multiplicity in analysis of primary outcome (efficacy of ILO compared with PBO) the primary comparison was between the Ilo10-16 mg/day group and the PBO group. If this test was significant at the 0.05 level, the subsequent pairwise comparison of the ILO 4-8 mg/day group with PBO would be considered significant at the 0.05 level. If the initial comparison was not significant, the Step-down comparison would not be considered significant, regardless of the nominal significance level. This Step-down design was not in the initial protocol but was added as an amendment.

Two-way analysis of covariance ANCOVA was used for the analysis of treatment main effect for continuous variables. The terms in the model included treatment, centre, baseline score and the treatment-by-baseline score term.

Two datasets were assembled, a LOCF and an OC. The primary efficacy evaluation was based on the LOCF dataset.

Subgroup Analyses. Analyses of efficacy in subgroups (RIS versus PBO) were conducted as above.

Secondary analysis of primary outcome. Analyses of continuous secondary efficacy variables were conducted as above. Categorical variables were analysed using Cochran-Mantel-Haenszel test, blocking on centres.

Population. All efficacy analyses were based on the ITT population. The ITT population included all randomised patients who received at least one dose of double-blind study medication during the initial double blind phase, and from whom at least one efficacy measurement (complete PANSS assessment) was obtained during that phase.

Adjustment for multiplicity. A Step-down approach was taken for the primary efficacy analysis to address multiplicity. No adjustments for multiplicity were carried out for secondary efficacy variables or secondary outcome analyses.

Note: Post hoc reanalysis using MMRM was conducted for this study for primary and secondary efficacy variable.

Results

Participant flow

Some 616 of 794 screened patients were randomised the study; 153 to ILO 4-8 mg/day, 154 to ILO 10-16 mg/day, 153 to RIS and 156 to PBO. Of these, 304 discontinued during Days 1-42: 52% ILO 4-8 mg/day, 44% ILO 10-16 mg/day, 42% RIS and 60% PBO. Table 13 gives the reasons for discontinuation.

Table 13. Reasons for discontinuation

	ILO 4-mg/d n-153 n (%)	ILO 10-16mg/d n=154 n (%)	RIS 4-8mg/d N=153 N (%)	PBO N=165 N (%)	Total n-616 n (%)
Primary reason					
Adverse experiences	5 (3%)	6 (4%)	12 (8%)	11 (7%)	34 (6%)
Treatment emergent adverse event	3 (2%)	6 (4%)	9 (6%)	10 (7%)	28 (5%)
Non-treatment emergent adverse event	2 (1%)	0	3 (2%)	1 (1%)	6 (1%)
Unsatisfactory therapeutic effect	36 (24%)	33(21%)	24 (16%)	64 (41%)	157 (25%)
Protocol violation	3 (2%)	3 (2%)	1 (1%)	0 (%)	7 (1%)
Withdrawal of consent	28(18%)	21(14%)	12 (8%)	14 (9%)	75 (12%)
Lost to Follow-up	7 (5%)	4 (3%)	14 (9%)	5 (3%)	30 (5%)
Death	0	0	1 (1%)	0	1 (0%)
Total Discontinued	79(52%)	67 (44%)	64 (42%)	94 (60%)	304 (49%)
Completed Protocol	74 (48%)	87 (56%)	98 (58%)	71 (40%)	312 (51%)

Conduct of the Study

Protocol amendments. There were several protocol amendments;

a) A main protocol amendment which changed the primary efficacy outcome variable from the PANSS-T to the BPRS,

b) The placebo run-in phase was extended by an additional 7 days. This was instigated because some patients appeared to clinically improve in the placebo run-in phase and investigators wanted to ensure this did not bias the placebo response.

c) Additional secondary study outcomes were added in a small number of sites and,

d) A Step-down analytical procedure was introduced from the 4-8 mg dose of Ilo.

Protocol compliance and CGP inspection findings. Sponsors note the existence of a GCP Quality Assurance Unit within the company that conducts audits of clinical research activities to evaluate compliance with the principles of GCP, however no information is provided regarding audits conducted or protocol compliance monitoring and performance in the conduct of this study.

Baseline data

There were no significant differences between treatment groups indicating successful randomisation (Table 14).

Table 14. Study 3004 Baseline demographics and clinical characteristics by treatment group

	ILO 4-8mg/d	ILO 10-16 mg/d	RIS	PBO
Demographics				
Age (mean, SD, range)	38.4±10.7 (19-64)	39.3±10.1 (18-66)	37.5±11.8 (19-66)	38.5±10.8 (17-67)
Sex (%male)	69%	71%	75%	67%
Race (%)				
Black	35%	31%	33%	37%
White	60%	59%	60%	57%
Asian	3%	5%	1%	1%
DSM IV Diagnosis				
Schizophrenia - Disorganized	19 (12%)	8 (5%)	11 (7%)	9 (6%)
Schizophrenia - Paranoid	81 (53%)	87 (56%)	83 (54%)	90 (55%)
Schizophrenia - Undifferentiated	23 (15%)	30 (10%	21 (14%)	20 (13%)
Schizoaffective	30 (20%)	29 (19%)	38 (25%)	37 (24%)
Baseline Clinical measures				
PANSS-T	95.4±15.2	93.4±16.2	94.5±16.3	94.1±16.1
PANSS-P	24.6±4.3	24.6±4.1	25.1±4.5	24.6±4.3
PANSS-N	24.1±5.9	23.0±6.0	23.4±5.6	23.2±5.8
PANSS-GP	46.8±8.8	45.7±9.5	46.0±9.8	46.2±9.3
BPRS	55.1±8.8	54.1±9.1	54.9±10.1	54.3±9.8
CGI-S	4.8±0.7	4.8±0.7	4.8±0.7	4.8±0.7

Compliance

Treatment compliance assessed by investigator and measured by capsule use (based on returned capsules) and feedback from patient, caregiver and study staff. Adequate treatment compliance was defined as the return of < 30% of prescribed study medication at the scheduled study visits. Treatment compliance ranged from 92-97% across all treatment groups. Proportion of patients with dose interruptions was low (<3% per treatment group).

Numbers analysed

Of the 616 patients randomised, 590 received at least one dose of study medication and had one complete efficacy measure obtained (143 ILO 4-8 mg/day, 149 ILO 10-16 mg/day, 146 RIS and 152 PBO.) These constitute the LOCF dataset. Of these, 310 patients completed the study (74 ILO 4-8 mg/day, 87 ILO 10-16 mg/day, 88 RIS and 61 PBO) and these comprise the OC dataset.

Primary outcome.

There was a significantly greater decrease in mean BPRS scores in the ILO 10-16 mg group and the 4-8 mg ILO group compared to PBO at study endpoint (Day 42 or premature discontinuation). Table 15 below summarises the results.

Note: Post hoc reanalysis using MMRM confirms the difference in score reduction between both ILO groups and PBO at study endpoint (ILO 4-8 mg/day: LS mead difference -3.66, 95% CI -7.07, -0.29, p=0.033; ILO 10-16 mg/day: LS mean difference -5.17, 95% CI -8.43, -1.91, p=0.002).

Secondary efficacy variables and analyses

There were significant differences between both ILO dosage groups and the PBO on decreases in PANSS –T, PANSS-P, PANSS-GP, CGI-S scores at study end (Day 42 or premature discontinuation), and for the ILO 10-16 mg/day group only in the PANSS-N. Table 15 provides details of comparisons between ILO groups and PBO on the primary and continuous secondary efficacy variables.

The proportion of patients with a ≥20% improvement in BPRS, PANSS-T, PANSS-N, PANSS-GP was not significantly different between either ILO dose group and the PBO. It was however significant for PANSS-P when comparing the ILO 10-16 mg/day and PBO groups.

There were significant differences between both ILO groups and PBO in proportion of patients who showed improvement in CGI-C (ILO 4-8 mg/day 77/153 (54%), ILO 10-16 mg/day 87/149 (58%), PBO 66/152 (43%), p=0.014 and 0.012, respectively).

Risperidone versus PBO

- *Efficacy variables*: The RIS group had a statistically significant greater decrease in score than PBO on all efficacy variables (BPRS, PANSS-T, PANSS.-P, PANSS-N, PANSS-GP, CGI-G). The mean difference in efficacy scale scores from baseline to endpoint is included in Table 15 for descriptive purposes. No statistical analyses were reported.
- Proportion of patients with a ≥20% improvement in BPRS, PANSS-T, PANSS-N, PANSS-GP and PANSS-P was significantly greater in the RIS group when compared to the PBO group.
- *CGI-C improvement*: A significantly greater proportion of the RIS group showed improvement in CGI-C when compared to the PBO group; PBO 66/152 (43%) and RIS 98/146 (67%); p<0.001.

Table 15. Change in primary (BPRS) and secondary efficacy variables at study end (day 42 or premature discontinuation) in ILO 4-8 mg/day, ILO 10-16 mg/day and PBO groups.

Analysis	ILO 4-8 mg/d (n= 153)	ILO 10-16 mg/d (n=149)	PBO (n=152)	ILO 4-8 vs. PBO LS mean, P value, 95% CI	ILO 10-16 vs. PBO LS mean, P value, 95% CI
	adjusted change	adjusted change			
BPRS*	6.2	7.2	2.5 (RIS 10.3)	LS mean: 3.8, P=0.012; 95% CI 0.9, 6.7	LS mean: 4.7, P=0.001; 95% CI1.8,7.5
PANSS-T	9.5	11.1	3.5 (RIS 16.6)	LS mean: 6.0, P=0.017; 95% CI 1.1,10.8	LS mean: 7.6, P=0.002; 95% CI 2.8,12.3
PANSS-P	3.5	4.1	16 (RIS 6.0)	LS mean: 31.9, P=0.02;	LS mean: 2.5, P=0.002;
				95% CI 0.3, 3.4	95% CI 0.9, 4.0
PANSS-N	1.9	2.4	1.0 (RIS 3.0)	LS mean: 1.0, P=0.133; 95% CI -0.3, 2.2	LS mean: 1.4, P=0.021; 95% CI 0.2,2.7
PANSS-GP	4.2	4.8	1.1 (RIS 7.8)	LS mean: 3.1, P=0.017; 95% CI -0.6, 5.6	LS mean: 3.7, P=0.003; 95% CI -1.2,6.1
CGI-S	0.6	0.5	0.2 (RIS 0.8)	LS mean: 0.4, P=0.003; 95% CI 0.1, 0.6	LS mean: 0.3, P=0.006; 95% CI -0.1, 0.6

Adjusted change = least squared mean change from the ANCOVA model (including 1treatment, centre, baseline and the treatment-by-baseline)
* Change is calculated as pre=post baseline so that a positive change indicates improvement.

Efficacy in Schizophrenia only Subgroup

In a post hoc analysis of the schizophrenia subgroup (n =484, 78% of the sample) neither ILO dose group was statistically significantly different from PBO (ILO 4-8 mg/day, LS mean -0.9, 95% CI -4.2, 2.3, p=0.58; ILO 12-16 mg/day, LS mean -1.7, 95% CI -4.8, 1.5, p=0.306). The RIS group was significantly different from PBO (LS mean -5.5, 95% CI -8.7, -2.2, p=0.001).

Note: This study was positive based on protocol defined outcomes, demonstrating a greater mean improvement in BPRS scores from baseline to study endpoint or early discontinuation in both the ILO 4-8 mg/day and 10-16 mg/day groups compared to PBO in a combined schizophrenia and schizoaffective study population. Based on this, the study was presented by the sponsor as one of the two positive efficacy studies required by the FDA for approval; however the FDA ultimately did not accept it as positive, based on post hoc analyses in the schizophrenia population.

Clinical studies in special populations

There have been no efficacy studies conducted in special populations. Clinical studies included only a very small number of participants over 65 years of age, and none over 75 years of age.

There have been no clinical studies in children. There is one study each in renal (ILP0103) and hepatic impairment (ILP0102), these studies are described above in the PK/PD section.

Analysis performed across trials (pooled analyses and meta-analysis)

See *Long-term studies* section below.

Supportive studies

PBO-controlled short term studies

Study ILP3000 was the first randomised, double-blind, PBO-controlled efficacy study. This study was negative in protocol defined outcomes but provides some supporting evidence of efficacy for the 12 mg/day dose. The primary objective was to determine the efficacy and safety of three fixed dosages of ILO (4, 8, and 12 mg/day) and haloperidol (HAL) 15 mg/day (7.5 mg bd) compared with placebo over 42 days in schizoaffective or patients with acute or subacute exacerbation of schizophrenia.

The primary efficacy outcome was the change from baseline to endpoint in PANSS-T. Randomisation and blinding followed the same protocols as Studies 3004 and 3005. The statistical methodology was also the same. To increase statistical power, the primary treatment comparison was between the average of the ILO 8 and 12 mg/day treatment groups versus PBO, and secondary comparisons including each ILO dose versus PBO. There was no adjustment for multiple testing. Efficacy analyses were conducted in an ITT population that comprised 573 patients (113 ILO 4 mg/day, 114 ILO 8 mg/day, 115 ILO 12 mg/day, 114 HAL and 117 PBO) and constituted the LOCF dataset.

Results. There was very poor retention in this study with 63% of patients discontinuing during Days 1-42: 57% of ILO 4 mg/day, 64% of ILO 8 mg/day, 58% of ILO 12 mg/day, 65% of HAL and 69% of PBO.

For the primary outcome there was not a statistically significantly greater reduction in mean PANSS-T scores in the ILO 8+12 mg/day group compared to PBO at study endpoint (Day 42)(p=0.065). Post hoc reanalysis using MMRM confirms this negative finding, with a p value of 0.255 for ILO 8+12 mg/day versus PBO in PANSS-T score.

Based on this primary negative finding, this study was overall negative. There was a statistically significant greater change in PANSS-T scores from baseline to endpoint in the HAL group compared to PBO.

In the secondary analysis there was a significant difference in PANSS-T scores between the 12 mg/day ILO dosage group and the PBO group (LS mean difference 5.2, 95% CI 0.1, 10.3, p=0.047) but there was no difference between the ILO 4 or 8 mg/day groups and the PBO group. Post hoc MMRM analysis failed to find a significant difference in PANSS-T score reduction for any ILO dose group (4, 8, or 12 mg/day) compared to PBO.

Schizophrenia versus Schizoaffective subgroup analysis

The post hoc ANCOVA analysis in the schizophrenia sub-group only (FDA results) was comparable to the results in the original sample: there was a difference for the 12 mg/day group (LS mean 6.7, p=0.037) but not 4 mg/day (LS mean 5.7, p=0.072), 8 mg/day (LS mean 1.4, p=0.67) or 8+12 mg/day (LS mean 4.0, p=0.15). HAL was different (LS mean 9.4,

p=0.005). Based on the original Step-down design the study remains overall negative in the schizophrenia only sub-group but provides some supporting evidence for the 12 mg/day dose.

Long-term Studies

A number of studies have been conducted to gather long term safety and efficacy data.

Two studies were extension phases of short term clinical trials (3000, 3004). The analytic methodology of these two studies was not suitable for assessing efficacy in maintenance (for further discussion see comments at the end of this section). Three other studies were designed as long term safety and efficacy trials (3001, 3002, and 3003). These latter three were identical in design, and on the advice of the European Medicines Evaluation Agency a protocol amendment was put in place while the studies were still in progress to change the primary efficacy analysis to a survival until relapse analysis in a pooled population from all three studies. A brief narrative description of the five studies and discussion follows.

Additionally open-label extension phases were conducted for VP 3101 and 3004. These are not discussed with respect to efficacy but provide safety data which is included in the *Safety* section below.

ILO 3004lt

This study was a multi-centre double-blind, active-controlled, parallel group, 52 week follow-up to an initial 6 week randomised, double-blind, placebo- and active-controlled multicentre efficacy and safety study. The objective of the long term phase was to explore long term safety and efficacy of ILO (4, 6, 8, 12, or 16 mg/day) as compared with that of RIS (2, 4, 6, or 8 mg/day) in patients with chronic schizophrenia (including schizoaffective disorder). ILO was administered in flexible dosing in 4, 8, 12 and 16 mg/day qd, the latter being included as part of a protocol amendment. Patients entered the study on completion of initial 6 week PBO-controlled double-blind phase, or if they were not benefiting from, or not tolerating their preceding phase treatment after completing 28 days. Primary efficacy measures were change from baseline to 52 weeks in scores on the PANSS-T, PANSS-P, PANSS-N, PANSS-GP, BPRS, CGI-C and CGI-S. Summary statistics and analysis are based on the Observed Cases dataset. Groups were comparable on baseline demographics and diagnoses. Compliance was considered good at 92-95% across groups. At Week 26, 51% of patients remained in the study. By Week 52, 23% of patients remained. The most common reasons for discontinuation were unsatisfactory therapeutic effect (33% ILO and 24% RIS) and withdrawal of consent (28% ILO and 31% RIS). Discontinuation for AEs was low (6% ILO and 8% RIS). In the observed cases dataset at Week 52, mean adjusted reduction from baseline in BPRS score was 23.5 for ILO and 23.7 for RIS. There were no differences between ILO and RIS groups in efficacy outcomes at Week 52.

ILO 3000lt

This study was practically the same as 3004lt in design, including assessments, endpoints and analytic plan. The major difference was that that the active comparator was HAL (5-20 mg/day) and there was a further 52 week open-label extension period (not described here). In terms of results, groups were comparable in demographics and diagnosis. Compliance was adequate at 80-90% across groups. There was a very high drop-out rate in this study: at Week 26, 30% (n=71) of participants remained in the study and by Week 51, 11% (n=26) of participants remained in the study (n=23 ILO, n=3 HAL). The most common reasons for discontinuation were unsatisfactory therapeutic effect (34%) for ILO and withdrawal of consent (35%) for HAL. Discontinuation due to adverse events (AEs)

was low (7-8%). Some 88% of the ILO and 83% of the HAL groups showed improvement on the CGI-C at Week 52 and there was a decline in mean PANSS-T scores from baseline to Week 52 in both groups. There were no differences between ILO and HAL groups in scale scores at Week 52.

ILO 3001, ILO 3002 and ILO 3003.

These three studies had identical protocols. All three were multi-centre, double-blind, 52 week prospective studies. After the studies were underway, the European Medicines Evaluation Agency advised that to demonstrate a long term maintenance effect, efficacy analysis should focus on time-to-relapse rather than mean changes from baseline. In light of this advice study protocols were amended to include a survival efficacy analysis of the combined data from the three. The amendments were released prior to study completion and database lock. The revised endpoints were then considered as the primary efficacy endpoints and replaced any previously planned analyses. The redefined objective of the studies was to compare maintenance of the antipsychotic effect of ILO 4-16 mg/day with that of HAL 5-20 mg/day in patients with schizophrenia or schizoaffective disorder over 46 weeks.

As a result of the amendment in the efficacy analysis, the analytic population was also redefined and the protocols amended. Patients were included in the analysis population if they completed an initial double-blind phase of 6 weeks, showed a reduction in the PANSS total score of at least 20% at Weeks 4 and 6 compared to baseline, had a CGI improvement score of less than 4, took at least one dose of long term double-blind study medication and had at least one efficacy assessment during the long term double blind phase. Primary outcome was survival time to first relapse. Survival analysis was conducted using a proportional hazards model with time to first relapse as the response variable and baseline PANSS total score and treatment group as independent variable. A difference between treatments of no greater than 15% in the proportion of patients having a relapse was not considered clinically important. Based on this it was calculated that ILO could be considered non-inferior to HAL if the upper bound the CI for the ILO hazard ratio was no greater than 1.676. This procedure is equivalent to a hypothesis test of non-inferiority (one sided) at the significance level of 0.025. Survival function of each treatment group estimated using the Kaplan-Meier product-limit method. The two survival functions compared using the Wilcoxon test and log rank test.

Relapse was defined as:

- An increase (worsening) of the PANSS total score of at least 25%, including at least a 10 point increase
- Discontinuation due to lack of efficacy
- Aggravated psychosis with hospitalisation (adverse event)
- A 2-point increase (worsening) of the CGI-C score after Week 6.

There were some differences between individual study populations; mainly in race due to the different study sites. Overall discontinuation rates were varied by study; Study 3001 - 30.5%, Study 3002 - 51.5% and Study 3003 - 58%. In the pooled dataset, proportions of patients who relapsed were: ILO 156/359 (43.5%) and HAL 47/114 (41.2%). In the time to relapse survival analysis, the hazard ratio (HR) for ILO was 1.03, 95% CI 0.743, 1.428. Thus, ILO is considered non-inferior to HAL as upper bound of HR confidence interval is below 1.676. There was no significant difference between the two in time to relapse (days); ILO 89.8±81.39 and HAL 101.8±89.36 (log rank test; p=.8411; Wilcoxon test, p=0.7637).

Evaluator Comment

All the above studies were conducted in compliance with GCP and had adequate assessment measures and schedules. However, Studies 3000 and 3004 do not have an appropriate design for assessing the efficacy of ILO as a maintenance therapy. The analytic method, of change in scale scores from baseline to study endpoint or discontinuation, does not assess relapse or recurrence. According to the EU guidelines[1], relapse is the re-emergence of symptoms after medication is stopped and recurrence is the re-emergence of symptoms after a period of being asymptomatic. The study population in these two extension studies were not patients who had been asymptomatic, and so recurrence cannot be assessed, nor were they patients who had stopped taking study medication so relapse cannot be assessed. This study informs us only that those who remained in the study on the study medications, continued to show improvements in scores from the baseline level. It is difficult without a PBO control group to delineate whether symptom improvements over the longer term indicate efficacy of the trial agent or are a reflection of the natural course of the disease. The EU guidelines do not require PBO control groups in long term maintenance comparator studies; however a PBO-controlled design would allow a more accurate characterisation of the efficacy in maintenance of trial drugs with respect to disease course. Moreover, these two studies had very high discontinuation rates and no data is provided characterising patients who discontinued compared to those who completed the study making it difficult to evaluate if drop-out was differential or random. In the light of these issues with patient discontinuation, the evaluator could not infer efficacy over time from data showing continuing improvement in the small number of individual who remained in the study, or given the design of the studies, efficacy as maintenance therapy.

The pooled Studies 3001, 3002, and 3003, using the revised study endpoint, sample, and analytic method are adequate for evaluating maintenance effect of ILO with respect to the comparator drug and do provide supportive evidence for the non-inferiority of ILO 4-16 mg/day to HAL 5-20mg/day with respect to time to relapse in maintenance treatment. Given that HAL is considered an effective drug for long term maintenance, this result provides the strongest evidence for long term use of ILO for maintenance. There is no adequate data available on comparability of ILO to RIS as maintenance therapy.

There is no long term efficacy data on the ILO 20-24 mg/day dose range as it was not included in any of these studies.

All of these long term double blind studies were conducted in mixed schizophrenia/ schizoaffective populations so no conclusions can be made regarding long term efficacy in schizophrenia only.

Evaluator's overall conclusions on clinical efficacy

Compliance with TGA adopted EU guidance documents

There are two instances where the studies submitted diverge from the EU guidance documents. The first (as outlined above) is that Studies 3000, 3004, and 3005 have mixed schizophrenia and schizoaffective samples contrary to the recommendations in the guidelines. The second is that the pivotal Study 3101, which only included patients with schizophrenia was only of 4 weeks duration rather than the recommended 6 weeks. Therefore none of the studies fully met the current EU guidelines but in most other respects the studies were designed and conducted in compliance with the guidelines. Of note, while an active comparator was included as a positive control in all short term double-blind PBO controlled studies, there were no two-way head-to-head comparator studies done with established anti-psychotic agents. Thus, comparative efficacy with

established agents has not been directly tested and caution should be exercised in making any such inferences from the data presented in the above trials.

Optimal dose ranges and dosage regimens

Schizophrenia only populations

There appears to be adequate evidence of efficacy for the upper dose range with two positive studies in schizophrenia only populations for 24 mg/day (3101 and 3005). For the remaining dose levels (12-16 mg/day), primary efficacy data based on protocol defined outcomes in schizophrenia only patients is available from one study only. Study 3005, in post hoc reanalysis showed superiority over PBO for doses between 12-16 mg/day and doses of 20 mg/day to 24 mg/day. There is secondary supporting data for the 12 mg/day dose from Study 3000 for the schizophrenia only population, however this study was negative based on protocol defined outcome and thus this secondary analysis cannot be attributed the same weight as evidence from the above two studies.

Mixed schizophrenia and schizoaffective populations

Based on protocol defined outcomes, Study 3004 provides primary efficacy evidence for the 12-16 mg/day range whereas Study 3101 provides it for the 24 mg/day range. For each dose, supporting evidence is available in secondary analysis from overall negative studies (3000 for 12 mg/day, and 3005 for 20-24 mg/day) and the same qualification made above stands.

ILO was administered bd in all Phase III trials. It can be taken with or without food and titration is required to get to steady state therapeutic dose.

Clinical relevance of the effect

Overall the decline in symptom scale scores, while significantly different from PBO, is modest in the mixed schizophrenia/schizoaffective populations. Decreases from baseline to study endpoint in PANSS-T scores that were significantly different from PBO (regardless of if these were primary or secondary analyses or from overall positive or negative studies based on protocol definitions) range from -9.5 to -14 points. Compared to other recently licenced antipsychotic agents, these changes in scores are towards the lower end of the spectrum of effect size: Invega range from -15.0 to -23.3, and Serdolect -9.5 to -23.8 (MIMS data).

The only data available in a schizophrenia only population, Study 3101, shows a decline in PANSS-T score from baseline to study endpoint of -12 points, within the range seen in the mixed population studies. The evaluator did not have data on the mean declines in scale scores for the schizophrenia only sub-groups from the other studies. However, data was available on the mean difference in change in scale scores from baseline to endpoint compared to PBO in those studies. Study 3005 and 3101 the mean differences in decline in PANSS-T in ILO compared to PBO at study endpoint ranged between -3.1 and – 4.9. This compares to -7 to -17.9 for Invega (data not available for Serdolect). Cohen's d for ILO 24 mg/day in Study 3101 was modest at 0.25.

Overall the data does indicate that ILO does have significant anti-psychotic efficacy over and above PBO, particularly for the higher dose of 24 mg/day but it may not convincingly be a very potent member of this class.

Adequacy of Study design

All four short term efficacy studies were appropriately designed to investigate efficacy. All trials included a PBO and active comparator group, although one pivotal study (3101) was only 4 weeks in duration rather than the 6 weeks recommended by the EU guidelines; a

shorter trial may affect the degree of treatment response. Active comparators in Studies 3000 (HAL), and 3005 and 3004 (RIS) where chosen according to the protocols on the basis of being widely used medications of known efficacy. HAL is a very old medication and is no longer widely used as a first-line treatment in schizophrenia. In the final study (3101), ZIP was chosen in part as it has a similar titration period to that required for Ilo. ZIP must be taken with food and the study protocol indicated that it was administered with breakfast in the mornings but did not specify administration with a meal in the evenings. In all studies, the randomisation method was robust and baseline demographics and clinical characteristics of treatment comparison groups did not differ significantly in any study, indicating successful randomisation. Mechanisms were in place to ensure that blinding was maintained.

Clinical relevance of outcome measures used

BPRS and PANSS-T are standard validated clinical scales for rating severity of psychotic symptomology and are widely used in efficacy trials in schizophrenia. CGI-C is a global clinical assessment of improvement.

Efficacy and safety in subpopulations

Safety in subpopulations is addressed in the *Safety* section below. There is no efficacy data available for children and the elderly. At the request of the FDA, the sponsor proposes a paediatric development plan to investigate PK, safety and efficacy in children ≥12 years and <18 years. The proposed completion time for that program is December 2014. There is no information provided on current status of that program.

Some 7-10% of Caucasians and a lesser proportion of African-Americans are poor (CYP2D6) metabolisers. Poor metabolisers have an approximately 2 fold increase in exposure to ILO and its active metabolite P88. Genotyping was used to identify metaboliser status of patients and the draft PI indicated that metaboliser status can be identified by laboratory tests. However, given that routine genotyping is not common clinical practice, the draft PI notes that clinical assessment of response must be mindful that metaboliser status will affect exposure and response.

One genetic polymorphism (CNTF) was investigated with respect to treatment efficacy, however this sub-study of Study 3101 had insufficient numbers to make comparisons of the efficacy of ILO in patients who were positive and negative for the polymorphism. It showed only that in patients who tested negative was ILO superior to PBO. Given that routine genotyping is not part of clinical practice, these findings are not relevant to this application.

Adequacy of the methods, conduct, analysis and reporting of results from main studies

The four short term PBO-controlled trials were all adequately designed and conducted. Analyses were carried out in accordance with pre-specified protocol defined outcomes and analytic methodologies, with most employing Step-down analytical plans in order to reduce the risk of type two error due to multiple testing. Reporting of results is detailed and comprehensive. However, many secondary analyses were undertaken, reported and presented as supporting evidence. The relative weight attributed to this evidence needs to take into account that there was no adjustment for multiplicity in any of the studies. For the long term double-blind studies, there are issues in the suitability of the study design and designated outcome measures in terms of assessing efficacy of ILO as maintenance therapy for the two double-blind long term phases of Studies 3000 and 3004. These are discussed above.

Based on the protocol defined outcomes, the primary efficacy findings are as the sponsor reported them. However, as indicated above, there are many secondary analyses and post hoc analyses, none of which are adjusted for multiplicity and the results of which are frequently cited as supporting evidence of efficacy. Related to this is the issue of head-to-head comparison with the active treatment in each study. The trials were not designed to undertake such comparisons. Furthermore, in material provided in response to FDA queries on relative efficacy of ILO and active comparators, the sponsors indicate that such analyses are not appropriate but should such post hoc comparisons be made, they must be adjusted for multiplicity and also for differences in titration.

Generalisability

The inclusion of schizoaffective patients in the trials needs to be considered. The proposed indication is for the treatment of psychotic symptoms in schizophrenia, so while the psychotic symptoms themselves may be the same as those in schizoaffective disorder, the sought indication is limited to schizophrenia.

As is usual in schizophrenia clinical trials, all studies all excluded patients with excess weight, substance abuse including alcohol, those requiring mood stabilisers and/or antidepressants and smokers, all of which are common in schizophrenia. This is standard practice and should not impact the external validity of these trials to any greater extent than trials of other medications in schizophrenia.

Special risk patients adequately studied to recommend dose adjustments?

There is adequate information on poor metabolisers to support recommended dose adjustments.

Is there sufficient long term data?

See discussion above on the adequacy of long term efficacy data. Long-term efficacy data are lacking for the ILO 20-24 mg/day dose. There is insufficient data to characterise dose experience by time.

Interactions

Specific studies examining the effect of interactions on efficacy have not been conducted. PK/PD studies adequately quantified effects of classes of drugs likely to produce interaction effects based on the main metabolic pathways of ILO and the effect of such interactions on efficacy can be inferred given the association between plasma concentration and efficacy shown in population PK studies (3001).

Time to relapse, disease progression, place among standard therapies

The only study examining time to relapse is the pooled analysis of Studies 3001, 3002, 3003, which show non-inferiority to HAL in terms of time to relapse over a period of 52 weeks. That study showed that mean time to relapse was 89.8 days for ILO and 101.8 for HAL. This difference was not statistically significant. However, there was substantial loss to follow-up in that study which makes it difficult to interpret in terms of effect of ILO on disease course. There is no data pertaining to disease progression. When evaluating the place of ILO among standard therapies, there is no direct data available from clinical trials of Ilo. While all short term double-blind studies included an active comparator, these trials were not designed as head-to-head comparator trials. The trials do provide descriptive data on the performance of each treatment arm with respect to PBO and to each other from which inferences can be made regarding comparative efficacy, however caution should be exercised in doing so. The studies were not designed for this purpose, and therefore differences in titration requirements can bias comparisons, and as multiple testing was not adjusted for, undertaking such a series of additional analyses increases the

risk of spurious findings. Numerical results of the active comparators on main efficacy outcome measures are presented above as descriptive data and informal comparisons can be made. The EU guidelines recommend two-arm head-to-head trials to establish relative efficacy, none of which were undertaken in the development program for ILO. Thus, evaluation of the place of ILO among standard therapies, should efficacy of ILO be demonstrated against PBO, should be based on safety and tolerability considerations at this time.

Overall evidence

Based on the evaluator's view that the appropriate indication is the "treatment of Schizophrenia" rather than the "psychotic symptoms in Schizophrenia", and EU guidelines that evidence for such an indication should be ascertained from study populations that do not include schizoaffective disorder, there is evidence of efficacy across the dose range for ILO in the treatment of schizophrenia. However, there are several issues that need to be weighed in determining if this evidence is sufficiently robust:

1. Other than the 24 mg/day dose, there is only one study supporting other doses in a primary outcome analysis, and all supporting data comes from studies that are overall negative.
2. The only trial conducted in a schizophrenia only population sample was only 4 weeks in duration.
3. The effect sizes are very modest, and although no formal head-to-head comparisons were conducted, currently marketed agents show greater numeric improvements in efficacy scale scores than ILO.

Evidence from the pooled long term studies does adequately demonstrate the non-inferiority of ILO 4-16mg/day to HAL as maintenance therapy. However, there is no data on long term efficacy as maintenance therapy for doses above 16 mg/day.

Sponsor's Clinical Overview

The sponsor's Clinical Overview draws too heavily on secondary outcome analyses for supporting evidence, particularly from studies which were not overall positive in the protocol defined outcomes. For example it states that two studies demonstrate efficacy of 12 mg/day dose and 24 mg/day dose; but in each case one of the two studies was overall negative and the analysis demonstrating efficacy is a secondary one.

Given that there was no adjustment for multiple testing in any of the clinical trials and that most were designed with Step-down primary and secondary objectives as the principal strategy to avoid type two errors, presenting of these results as evidence of efficacy without qualification is problematic.

Safety

Introduction

The Integrated Safety Database (ISD) comprises integrated safety data from 9 studies (2001, 2328, 3000, 3001, 3002, 3003, 3004, 3005, and 3101). The Integrated Safety Summary (ISS) presented in the application materials presents safety data for four different groupings these studies:

Group 1) All patients from the controlled phase (PBO and/or active comparator) of all nine trials;

Group 2) Data from the short term PBO-controlled phase of the 4 double-blind, PBO-controlled trials 3000, 3004, 3005, and 3101;

Group 3) Eight of the 9 trials in Group 1, Study 2328 being omitted as it was not blinded; and

Group 4) Data from the open-label extension phases of 2001, 3000, 3001, 3002, 3004 and 3005.

In terms of selecting the datasets most relevant to evaluating the specific terms of the current application, the evaluator focussed on short term PBO-controlled studies (Group 2) and the long term double-blind studies (Group 3) as the principal sources of data. For the longer term safety data, the evaluator elected Long-term safety data Group 3 in preference to Group 1 which is the primary dataset used by the sponsor, on the rationale that Study 2328 was not double-blind and was designed specifically as a safety study to examine QTc effects, both of which might affect the way in which AEs are ascertained. Open-label data is taken from both Group 4 above, and the open-label phase of 3101 which was not completed when the Integrated Safety Database was compiled.

The Integrated Safety Database (ISD) groups ILO data into three dose groups for analysis ILO (4-8 mg/day, 10-16 mg/day and 20-24 mg/day) and the ISS presents safety data for all ILO dose combined and by each dose groups. These groupings reflect the dosing regimens of the component studies and 10-16 mg/day group is slightly wider than the dose range being sought in the application, where 12 mg/day is the lowest dose. For the purposes of evaluating this application, the evaluator focussed primarily on the two higher dose groups: ILO 10-16 mg/day and ILO 20-24 mg/day, and when citing values for the combined ILO group, unless otherwise stated, refers to these two dose groups combined only. The rationale for this approach is that the ILO 4-8 mg/day dose has not shown efficacy and is not being recommended by the sponsor for use. Moreover, including this dose group in a combined ILO group has the potential effect of biasing the estimates downwards if adverse effects are dose related. Results from the ILO 4-8 mg/day group will be included where relevant.

Neither of the longer term datasets described above (ISS Groups 1 and 3) are informative regarding dose-related safety over the long term as fewer than 25% of patients taking ILO 20-24 mg/day were exposed for longer than 4 weeks and only 19 patients were exposed beyond 6 weeks. Thus, the short term PBO-controlled trial dataset is the principal source of dose-related information (and indeed as the main trial to use the 20-24 mg/day dose (3101) was only 28 days compared to 42 for the other three, endpoint data from this group needs to be interpreted with care). ZIP was an active comparator in only one trial lasting 4 weeks (3101), and thus comparative safety data for ZIP is only relevant to short term use. PBO control was only used for a maximum of 6 weeks, and given that patients will have been exposed to study-drugs for considerably longer in some cases and that AEs tend to emerge over time, the evaluator did not make direct comparisons with PBO for long term ILO data. Thus, safety data for the longer term drawn from these studies will be presented for the ILO 10-16 mg/day group, HAL and RIS only.

For open-label studies, the pooled ISD data is drawn mainly from studies using the lower dose ranges, with a mean dose of 11 mg/day, and in the open-label phase of Study 3101 the mean dose was 21 mg/day, offering some limited comparison between dose groups over longer time periods. However, interpretation of these data must be circumspect due to the imprecision of dosing data, the limitations of open-label study design, including high levels of discontinuation and so on.

With the exception of Study 3101, all studies in the ISD included both patients with schizophrenia and schizoaffective disorder. In the short term PBO-controlled dataset ~14% in the combined ILO group were schizoaffective (21.1% ILO 10-16 mg/day and 6.4% ILO 20-24 mg/day) and 20.4% of PBO, 38.1% of HAL and 22.5% of the RIS groups. All ZIP patients had schizophrenia. In longer term data, 11.4% of the ILO 10-16 mg/day group and 12.6% of the HAL and 22.5% of the RIS groups had a schizoaffective diagnosis. The methodology used to evaluate the safety of the studies was appropriate. Assessments were done at minimum baseline and end of study/early termination. The normal laboratory ranges and criteria for potentially clinically significant abnormal values were defined in the protocols and were consistent across studies. Adverse events were in the majority of cases assessed at each study visit and the remaining recorded at any time in the study period when they came to notice. AEs were assessed by patient self-report, the investigator or identified by abnormal laboratory values. Limited statistical analysis was undertaken in the ISS. Being mindful of the potential for spurious findings when performing multiple analyses in large datasets such as these, the evaluator nonetheless felt that some statistical testing was informative. The evaluator undertook some limited categorical analyses using Cochran-Mantel-Haenszel chi squared statistic to compare the PBO and ILO groups or the ILO dose groups for adverse events that were considered relevant.

ILO received approval in May 2009 in the USA and has been commercially available but no post marketing data was included with the current submission.

Patient exposure

The cut-off date for the Integrated Safety Database was 4 December 2006. Baseline patient characteristics were similar across all eight studies (long- and short term). The majority of patients were male and younger than 50 years. There was some variability in ethnicity due to the multi-site designs of the majority of studies. The majority of patients being White, except for the ZIP group where half the subjects were Black and another 13% Asian (Note: ZIP was only used in one short term placebo-controlled study; 3101). The majority of study subjects were diagnosed with psychosis before age of 25 and fewer than 4% diagnosed after 45 years. The majority had a paranoid subtype diagnosis (PBO 66.6%, ILO 61.5%, HAL 59.7%, RIS 60.5% and ZIP 84.7%), while fewer had the undifferentiated subtype (PBO 9.0%, ILO 13.1%, HAL 11.7%, RIS 11.8%, 13.3 ZIP %), with smaller percentages of disorganised, catatonic and residual subtypes. The proportion of schizoaffective disorder patients is described above.

Exposure to Study Drug

Overall in the eight studies, 2764 patients were exposed to ILO (n=948 to 4-8 mg/day, n=1425 to 10- 16 mg/day, and n=391 to 20-24 mg/day) for a combined total duration of 1019.59 patient years (267.24, 722.62 and 29.72 patient years for ILO doses 4-8 mg/day, 10-16 mg/day, and 20-24 mg/day respectively). Tables 16 and 17 below give details of pooled patient exposure to study drug in the relevant ILO and comparator dose groups. As mentioned above, in the main analysis that follows the ILO 4-8 mg/day group generally will be omitted as approval is not being sought for this dose level and it is not within the recommended treatment range. Where relevant or informative that dose will be included and noted. Of note, for the ILO 20-24 mg/day dose there was very limited exposure beyond 6 weeks: n=98 patients exposed >4 to ≤5 weeks, n=72 for >5 to ≤6 weeks and n=15 for >6 weeks, thus, discussion of ILO in the long term will refer only to ILO 10-16 mg/day patients unless otherwise stated.

Table 16. Total patient exposure to study drugs, number x patient years.

Treatment group	Patient Ns	Patient Years
Short-term PBO controlled		
PBO	587	41.71
Combined ILO	874	71.31
ILO 10-16 mg/d	483	41.59
ILO 20-24 mg/d	391	29.72
HAL	118	8.13
RIS	306	28.21
ZIP	150	9.17
Long-term double-blind		
ILO 10-16 mg/d	1425	722.62
HAL	546	261.57
RIS	306	56.12

In the pooled open-label Study 1042 patients received ILO treatment for a period of 997.4 patient years and in Study 3101 in the open-label phase, 173 patients received ILO treatment for a period of ~37 patient years.

Table 17. Overall patient exposure to study drugs, number and patient years

	PBO (n=587)	ILO 10-16* mg/d (n=1425)	ILO 20-24 mg/d (n=391)	All ILO (n=1816)	HAL (n=546)	RIS (n=306)	ZIP (n=150)
> 1 week	507 (86.4%)	1385 (97.2%)	387 (99.0%)	1722 (97.6%)	499 (91.4%)	280 (91.5%)	135 (90.0%)
> 4 weeks	225 (38.3%)	1224 (85.9%)	98 (25.1%)	1322 (72.8%)	408 (74.7%)	224 (73.2%)	4 (2.7%)
> 6 weeks	35 (6.0%)	949 (66.6%)	15 (3.8%)	964 (53.1%)	345 (63.2%)	96 (31.4%)	0
> 3 months	0	748 (52.5%)	0	748 (41.2%)	284 (52%)	46 (15%)	0
> 6 months	0	624 (45.1%)	0	624 (34.4%)	236 (43.2%)	36 (11.8%)	0
> 12 months	0	71 (5.0%)	0	71 (4.1%)	24 (4.4%)	6 (2.0%)	0

Source Table 16, ISS page 61.
*The difference from Table 4.1 in N for weeks 1-6 in the ILO 10-16 mg/d, RIS and HAL groups, is because Table 4.2 includes short-term data from the double-blind, non-PBO controlled short-term phases of the longer term studies in addition to the PBO-controlled short-term study data.

Average duration of exposure in open-label studies was 349.6 days in pooled studies and 103 days in Study 3101.

Adverse events

Overview

AE data is described based on a short term dataset comprising data from the 4 double-blind PBO controlled studies for the following groups: ILO 10-16 mg/day and ILO 20-24 mg/day separately and combined, PBO, RIS, HAL and ZIP. An extended dataset comprising data from four double-blind long term studies and ILO 10-16 mg/day, HAL, and RIS data from the PBO-controlled studies in the short term dataset. Duration data is be drawn from this latter dataset, however in terms of overall frequencies of AEs over the longer term

that dataset is informative for ILO 10-16 mg/day, HAL and RIS only, as it contains no additional data for PBO, ILO 20-24 mg/day and ZIP beyond 4-6 weeks.

Discontinuation

In the short term (<6 weeks) overall discontinuation percentages across treatment groups were lower than PBO for all active agents while discontinuations due to AEs were more frequent in all active treatment groups than PBO, with the exception of the ILO 10-16 mg/day group. In the longer term overall discontinuations were similar in the HAL and ILO 10-16 mg/day groups, both of which were lower than RIS, while discontinuations due to AEs were lower in ILO 10-16 mg/day than either comparator. Table 19 gives discontinuation frequencies for in the short and longer term.

Table 19. Discontinuations and discontinuations due to AEs

	PBO	ILO 10-16 mg/d	ILO 20-24 mg/d	HAL	RIS	ZIP
Short-term <6 weeks						
Overall Discontinuations	52.5%	22.1 %	28.2%	31.3%	34.6%	34.7%
Discontinuations due to AEs	11.0%	10.4%	16.2%	17.8%	17.9%	25.0%
Long-term >6 weeks – 12 months						
Overall Discontinuations	n/a	45.8%	n/a	45.1%	77.6%	n/a
Discontinuations due to AEs	-	6.9%	-	15.5%	11.5%	-

In open label, 46.0% in the pooled studies discontinued, 10.4% due to an AE. Some 58% discontinued in Study 3101, of these, 23.8% were due to an AE.

Frequency, drug-related, severity and treatment duration relation of AEs.

Overall the most commonly affected System Organ Classes (SOCs) for all patients were Nervous system, Psychiatric disorders and Gastrointestinal disorders. The majority of AEs across treatment groups were mild to moderate in severity and the majority of severe AEs occurred in only 1 or 2 patients per treatment group.

Short-term dataset

- In short term PBO controlled studies, overall the combined ILO group 709 patients reported 2805 treatment emergent AEs, representing 80.8% of ILO treated patients reporting one or more adverse events. This number is numerically but not statistically significantly higher than PBO (75.1%) (M-H = 0.837, p=0.3603), and not statistically significantly different from comparators (HAL 94.9%, RIS 78.4%, ZIP 86.7%).
- Comparing by dose, there was no statistically significant difference between the ILO 20-24 mg/day group (84.1%) and the ILO 10-16 mg/day group (78.3%) in number of patients with one or more AE (MH=0.509, p=0.47556).
- For ILO treated patients, AEs that occurred more often compared to PBO, and at a rate of ≥ 1% in either dose group or both combined, were in the Gastrointestinal disorder, Nervous system, Cardiac, Psychiatric disorders and Reproductive SOCs.
- In the combined ILO group. 49.6% (1390/2805) of AEs were considered by investigators to be drug related, with 54.7% of all ILO patients (41.2% of PBO, 66.1% of HAL, 57.4% of RIS, and 78.7% of ZIP patients) having ≥1 drug related AE.
- The ILO 20-24 mg/day group had a greater proportion of patients with 1 or more drug-related AEs than ILO 10-16 mg/day (68% versus 43.9%).
- The most commonly reported drug-related AEs occurred in the Nervous system, Gastro intestinal disorders and Investigations SOCs. AEs adverse events were

considered drug-related in ≥5% of either ILO 20-24 mg/day or ILO 10-16 mg/day patients were tachycardia constipation, dry mouth, nausea, weight increase, dizziness, headache, sedation and somnolence.

- In the short term dataset, 2.2% of AEs reported were severe, with 11.5% of ILO patients reporting one or more severe AE. This was similar to PBO (13.5%), ZIP (10.1%) and RIS (10.1), all of which were lower than HAL (23.7).
- The ILO 10-16 mg/day group had more severe AEs than the ILO 20-24 mg/day group (12.8 versus 5.6%)

Long-term dataset

- Some 85.1% of the ILO 10-16 mg/day reported at least one AE (compared to 92.1% in the HAL and 80.7% in the RIS groups), most commonly occurring in Psychiatric disorder, Gastrointestinal disorders and Nervous system disorder SOCs.
- Some 49.5% of the ILO 10-16 mg/day group had an AE considered drug-related by investigators (HAL 70.7%, and RIS 49.7%).
- Most commonly drug-related affected SOCs were Psychiatric disorder, Nervous system and Gastrointestinal disorders. However, only 3 AE occurred in ≥5% of ILO treated patients in these SOCs: insomnia, dizziness and headache.
- Some 8.7% of all AEs were considered severe, with 19.5% of ILO 10-16 mg/day group with an AE having one or more severe AE (compare to 23.7% of HAL and 8.0% of RIS groups).

Open-label

- In the pooled open-label studies, 69.4% of all ILO treated patients had at least one treatment emergent AE. The most frequently reported AEs were insomnia (13.4%), anxiety (11.6%), psychotic disorder and schizophrenia (both 8.3%), depression (5.5%), headache (6.3%), dizziness (5.5%) and nasopharayngitis (4%). Some 32.6% of AEs were suspected to be related to study medication.
- In Study 3101, 73.4% of all ILO treated patients had at least one treatment emergent AE. The most frequently reported AEs were headache (13.9%), weight increase (9.2%), dizziness (6.9%), nausea and sedation (6.4% each), insomnia (5.2%), nasopharayngitis (4.6%) and dry mouth (4%). Some 54.9% of AEs were suspected to be related to study medication.

AEs in relation to duration of treatment

Duration data is taken from the expanded longer term dataset, thus there will be little or no duration related data on ILO 20-24 mg/day and ZIP beyond 4 weeks or PBO beyond 6 weeks. Overall, the majority of AEs occurred early in treatment; 80.6% of the combined ILO group experienced AEs during first 6 weeks of treatment, which was comparable to PBO (74.8%). In the first six weeks of exposure, the ILO 20-24 mg/day group reported more AEs than the 10-16 mg/day group (84.1% versus 72.8%). For the ILO 10-16 mg/day dose group the incidence of AEs reported between 6 weeks to 6 months, 6 – 12 months and > 12 months were 55.1%, 49.2% and 31%, respectively.

In pooled open-label studies the incidence of AEs was 38% for 0-6 weeks, 41.2% for >6 weeks to 6 months, 37.2% for >6 months to 12 months and 35.9% for > 12 months.

Major AEs by SOC

More detailed information provided on AEs prioritised those SOCs and AEs which are known to have greater adverse effects across this class of drugs in order describe ILO in the context of currently available drugs: extrapyramidal symptom (EPS), metabolic parameters, weight gain, and sedation.

Nervous System Disorders

In short term PBO-controlled dataset, more ILO treated patients than PBO patients reported an AE (43.6% versus 35.3%) (MH=4368, p=0.036). However, the proportion was lower than in the HAL, RIS, and ZIP (70.3%, 47.4%, and 62.7% respectively) groups. There was no significant difference between the two dose groups**.**

In particular: the combined ILO group had higher frequencies than PBO of dizziness (14.5% versus 7%, p<0.001), sedation (6.7% versus 3.1%, p= 0.0033), numerical but non-significant difference for somnolence (5.5% versus 2.4%, non sig) and tremor (2.7% versus 1.9%), and a numerical difference, but too low an overall incidence to meaningfully compare, for muscle rigidity (1.0% versus 0.2%).

When comparing ILO doses, the ILO 20-24 mg/day group had higher incidence of dizziness (19.7 versus 10.4) and sedation (10.2 versus 3.9) than the ILO 10-16 mg/day dose group, while the ILO 10-16 mg/day group had higher frequencies of lethargy, paraesthesia and postural dizziness than the higher dose group.

The ILO combined group had a lower proportion of patients reporting akathisia AEs than PBO (1.9% versus 2.7%), and it was also considerably lower than comparators HAL 13.6%, RIS 6.9% and ZIP 7.3%.

For EPS as a composite term in short term data, 13.5% of the ILO 10-16 mg/day group and 15.1% of the ILO 20-24 mg/day group had an EPS AE, compared to 11.6% in PBO, 53.4% in HAL, 28.1% in RIS and 24.0% in ZIP. Both ILO dose groups were lower than PBO with respect to akathisia, while the ILO 10-16 mg/day group was higher on tremor and EPS and the ILO 20-24 mg/day group was lower. Both ILO groups were lower than all active comparators on EPS, tremor, akathisia, postural dizziness.

Long-term exposure to ILO 10-16 mg/day resulted in fewer nervous system AE reports than long term exposure to both HAL and RIS for extrapyramidal disorder, tremor, akathisia, muscle rigidity and dystonia. HAL also had a higher incidence of somnolence and dyskinesia whereas RIS had more bradykinesia.

With respect to duration of treatment, for ILO treated patients Nervous system AEs were highest in Week 1 and these had decreased substantially by Weeks 5-6 (ILO 10-16 mg/day 22.6% to 8.5%, ILO 20-24 mg/day 32.5% to 11.2%). A similar pattern of decline from Week 1 to Weeks 5-6 occurred in all other treatment groups (PBO 23.0 to 8.9%, HAL 41.5% to 13.5, RIS 27.1 to 13.4% and ZIP 47.3 to 25%). Over the longer term, frequencies of AEs in the ILO 10-16 mg/day group were 8.7%, 9.1%, 15.6% over the 6 weeks - 3 months, 3-6 month, 6-12 month periods, respectively (HAL 19.1%, 18.0%, and 14.8%, RIS 13.5%, 17.4%, and 13.9%, respectively).

Nervous system disorder AEs were more often considered drug-related in the combined ILO group (32%), compared to PBO (22.3%) but similar to RIS (33.0%) and less often than that of HAL and ZIP (54.2% and 59.3%, respectively). There was a higher frequency in the ILO 20-24 mg/day group than the ILO 10-16 mg/day group (41.2% versus 24.6%) of AEs which were considered drug related. Dizziness and headache were more often considered drug-related in the ILO 20-24 mg/day group compared to all other groups with the exception of ZIP. Dizziness, headache, sedation and EPS were considered drug-related

more than twice as often in the ILO 20-24 mg/day group than the ILO 10-16 mg/day group. In the long term, 28.6% of nervous system AEs in the ILO 10-16 mg/day group were considered drug related which can be compared to 34.6% in the RIS group and 59.3% in the HAL group.

Only 1 (0.2%) ILO treated patient (10-16 mg/day group) discontinued due to EPS in the short term studies and this was lower than PBO (0.3%), HAL (2.5%), RIS (1.3%), and ZIP (2.0%). In the longer term, no further ILO or RIS patients discontinued due to EPS, while for HAL the proportion that discontinued due to EPS rose to 5.3%.

In the open label studies, 25.9% of ILO treated patients in pooled studies and 37% of ILO treated patients in Study 3101 had nervous system AEs. The most common AEs reported including headache, dizziness, somnolence, sedation and tremor. The frequencies were similar across both sets of data, suggesting no notable dose differences.

Additional EPS measures

EPS Symptoms Rating Scale

In PBO-controlled studies, the percentage of patients who had a worsening score from baseline to endpoint was similar between combined ILO groups (24.9%; ILO 10-16 mg/day 26.4%, ILO 20-24 mg/day 23.2%), PBO (25.5%) and ZIP (25.3%) but much lower than the HAL group (61.4%) and somewhat lower than the RIS group (34%).

Barnes Akathisia Scale[10]

In the PBO-controlled studies, 7.7% of the combined ILO group had a worsening change from baseline to endpoint in their global clinical assessment of akathisia score. The ILO 10-16 mg/day group was somewhat higher than the ILO 20-24 mg/day group (9.5 versus 5.9%). ILO was lower than the comparators (PBO 13.3%, RIS 18.9%, and ZIP 21.1%).

In longer term data, 9.2% of the ILO 10-16 mg/day group had a worsening score from baseline to endpoint, however the HAL group had much higher proportion of patients who worsened (25%) and the RIS group result was intermediate (16.6%) in this respect.

Overall ILO causes few EPS side effects and has a favourable profile compared to the active comparators.

Investigations SOC

Weight increase AEs are discussed in the section *Vital Signs*.

Heart rate increase

In the short term dataset, increased heart rate was reported more frequently in the combined ILO group (2.9%) compared to PBO and the active comparators (PBO 0.2%, HAL and RIS 0%) except ZIP (5.3%). This increase in the combined ILO group was due to the ILO 20-24 mg/day group (5.1% compared to 0.8% in ILO 10-16 mg/day). Heart rate increases (AE) were considered drug-related more frequently in the ILO 20-24 mg/day group (4.6%) than the PBO (0.2%), ILO 10-16 mg/day (0.8%), ZIP (4.7%) and RIS (0.0%) groups.

Where the combined ILO group had more than twice the frequency of PBO for other AEs which were reported with a low incidence (≥5 individuals) these included increases in

[10] The Barnes Akathisia Scale (commonly known as BAS or BARS) is a rating scale that is administered by physicians to assess the severity of drug-induced akathisia.

blood creatine phosphokinase and alanine aminotransferase (ALT). In both instances it was the ILO 20-24 mg/day group which had a frequency that was double that of the PBO group, while the ILO 10-16 mg/day group was the same or lower than that of the PBO group. Other AEs which were considered drug-related and reported more frequently in the ILO 20-24 mg/day group include increases in ALT and blood creatine phosphokinase levels.

Psychiatric disorder

Short-term: overall Psychiatric disorder AEs were reported in 34.3% of ILO treated patients (ILO 10-16 and 20-24 mg/day) compared to 39.7% in PBO (no significant difference), 38.9% RIS, 27.3% ZIP and 58.6% HAL. In particular, there was a higher frequency in the combined ILO group compared to PBO in depressed mood (1.1% versus 0.3%) and nightmares (1.1% versus 0.2% respectively). By ILO dose, Psychiatric disorder AEs were reported more frequently in the ILO 10-16 mg/day group than the ILO 20-24 mg/day group (42.9% and 23.8% respectively). Schizophrenia was reported more frequently in the ILO 10-16 mg/day group (5.4%) compared to the ILO 20-24 mg/day (2.3%) group, PBO (4.1%), HAL (2.5%), RIS (2.7%) and ZIP (0.7%) groups. Psychotic disorders were also more frequent in the lower dose group than the ILO 20-24 mg/day group (3.7 versus 1.8%), with the following results in the other groups: PBO 2.7%, HAL 5.1%, RIS 1.0% and ZIP 2.0%. In the longer term, 56.3% of the ILO 10-16 mg/day group reported a Psychiatric disorder AE, which was higher than the RIS (43.1%) group but lower than the HAL (62.6%) group.

In the short term, PBO-controlled dataset Psychiatric disorder AE were considered drug-related in 11.4% and 10.7% of the ILO 10-16 mg/day and 20-24 mg/day groups, respectively, with the following results in the other groups: PBO 10.6%, HAL 22.9%, RIS 9.2% and ZIP 16.7%. In both the short and long term, the HAL group had a higher frequency of Psychiatric disorder AEs considered drug-related than all other treatment groups.

Cardiac Disorder

In the short term PBO-controlled dataset, cardiac AEs were reported by 7.2% of the combined ILO group higher than PBO (2.6%, MH 14.12, $p<0.001$), HAL, RIS, and ZIP (1.7%, 1.6% and 4.0% respectively). In particular tachycardia, palpitations and sinus tachycardia occurred more frequently in combined ILO group compared PBO and tachycardia more frequently than all other comparators. Overall cardiac AEs were more frequent in the ILO 20-24 mg/day group than the ILO 10-16 mg/day group (11.8 versus 3.7%), specifically tachycardia (7.7% versus 2.5%) and sinus tachycardia (1.3% versus 0%), although the overall incidence was very low for the latter.

In PBO-controlled studies cardiac disorder AEs were more often considered drug-related in ILO treated patients than in all other treatment groups (ILO 7.2%vs 1.0%- 4.0%). There was dose related difference in drug-related cardiac AEs: 10-16 mg/day 3.1%, and 20-24 mg/day 11.3%. Tachycardia was more frequent in the ILO 20-24 mg/day group than the ILO 10-16 mg/day group (7.7 versus 2.5%).

In the longer term, 4.4% of ILO 10-16 mg/day patients had a cardiac AEand this can be compared to 2.9% of HAL and 2.3% of RIS patients.

Vascular Disorder

In the short term PBO-controlled dataset, the combined ILO group had a higher percentage reporting AEs than PBO (6.2 versus 3.1%)(MH 6.612, $p=0.01$) and comparator agents (0.7-4.2%). Specifically orthostatic hypotension and hypotension were more frequently

reported in the combined ILO group than the PBO group (3.8 versus 1.2% and 1.5% versus 0.3%, respectively) and both were more frequent, but not statistically significantly so in ILO 20-24 mg/day group than the lower dose group (orthostatic hypotension 4.9% versus 2.9% %; hypotension 2.6 versus 0.6%). There were no cases of orthostatic hypotension or hypotension in HAL or ZIP and 1.0% and 0.3%, respectively in RIS. Hypertension was more frequently reported in HAL than other treatment groups. With respect to duration of treatment, for hypotension ILO was similar to all treatment groups by Week 6, similar to HAL in the 6-12 month period and not reported at all beyond 12 months. In double-blind long term studies, 5.3% of ILO 10-16 mg/day patients reported vascular AEs compared to 3.8% and 4.2% of HAL and RIS patients, respectively. In long term data, orthostatic hypotension was reported in 2.5% of ILO 10-16 mg/day patients, 0.7% of HAL patients and 1.3% of RIS patients. In open-label studies orthostatic hypotension was reported in 1.5% of all ILO treated patients.

In the short term, overall vascular disorder AEs were considered drug-related more frequently in the ILO groups (ILO 10-16 mg/day 3.7%, ILO 20-24 mg/day 6.6%) compared with other treatment groups (0.0% to 2.2%). Orthostatic hypotension and hypotension were more frequently considered drug-related in ILO treated patients, particularly in the 20-24 mg/day group, compared to PBO and all the active comparators. In longer term data, 3.8% of the ILO 10-16 mg/day vascular AEs were considered drug-related, compared to 2.2% in HAL, and 1.6% in RIS.

Gastrointestinal Disorder

In short term PBO-controlled studies, 34.8% of ILO combined group (ILO 10-16 and 20-24 mg/day) reported AEs compared to 32.5% of PBO patients, with no difference between ILO dose groups in frequency. Frequencies in active comparators were HAL 39.8%, RIS 34.3% and ZIP 46.0%. Dry mouth was the only AE reported more frequently in the combined ILO group compared to PBO (8.6% versus 1.2%, p=0.05) The ILO 20-24 mg/day group had higher frequencies for most gastrointestinal AEs than the ILO 10-16 mg/day group, PBO and at least one other comparator. Nausea was more frequent in the ZIP group than any other comparison group. In the longer term, 26.8% of ILO 10-16 mg/day patients had a Gastrointestinal AE, compared to 26.7% in HAL and 37.3% in RIS.

In the short term, gastrointestinal AEs were considered drug-related in 16.1% of ILO 10-16 mg/day and 27.4% in ILO 20-24 mg/day compared to 15.0% PBO, 10.2% HAL, 10.1% RIS, and 36.7% ZIP.

General Disorders and Administration Site Conditions

In short term data, ILO treated patients had a higher frequency, though not statistically significantly different, than PBO (14.5% 10.7%) whereas the active comparators were comparable to ILO (HAL 15.4%, RIS 10.1%, and ZIP 12.0%). There were no differences between the two ILO dose groups. Incidences were low, but there was a higher frequency in the combined ILO group compared to PBO for irritability (1.4 versus 0.7%) asthenia (1.4% versus 0.5%), and pyrexia (1.0% versus 0.3%). The ILO 20-24 mg/day group had a significantly higher frequency of fatigue than PBO (6.1% versus 3.2%) and was numerically but not statistically higher than the ILO 10-16 mg/day (4.3%) group. There was also a higher frequency of pyrexia and chest pain in the ILO 20-24 mg/day group compared to the PBO and ILO 10-16 mg/day groups.

Musculoskeletal and Connective Tissues Disorders

In the short term, there was no statistically significant difference between the combined ILO group and PBO in AEs (15.2 versus 14.1%). Compared to the active comparators, the combined ILO group was lower than HAL 24.6%, higher than RIS 11.8% and comparable to ZIP 17.3%. The ILO 20-24 mg/day group reported AEs more frequently than ILO 10-16 mg/day (17.9% versus 13.0%) but the difference was not significant. Musculoskeletal stiffness was reported more frequently in the combined ILO group than PBO (1.9% versus 1.0%) and was higher in the ILO 20-24 mg/day group than ILO 10-16 mg/day group (2.8% versus 1.2%). In the longer term, the frequencies of AEs were ILO 10-16 mg/day 12.7%, HAL 22.3%, RIS 14.4%. By ILO dose groups, musculoskeletal stiffness and muscle twitching were more frequent in ILO 20-24 mg/day than the lower dose group and PBO.

Overall musculoskeletal AEs were considered drug-related more often in the combined ILO, HAL and ZIP groups compared to the PBO and RIS groups, and the frequency of AEs which were considered drug-related was higher in the ILO 20-24 mg/day group compared to the lower dose group (10% versus 2.3%).

Renal and Urinary disorder

Overall in the short term PBO-controlled data, AEs were reported more frequently in the combined ILO group than the PBO (3.3 versus 1.4%), it was marginally significantly (MH=3.783, p=0.052), and similar with respect to active comparators (HAL 2.5%, RIS 1.6% and ZIP 4.7%). Specifically, urinary incontinence occurred in 1.3% of ILO treated patients compared to 0.7% of the PBO patients and 0-0.1.7% of the active comparator groups. Pollakiuria was higher in the ILO 20-24 mg/day group (1.0%) than the ILO 10-16 mg/day (0.2%) and PBO (0.3%) groups, and stress incontinence followed the same pattern (1.0% ILO 20-24 mg/day and 0% ILO 10-16 mg/day and PBO). All these had a low incidence.

Reproductive system and breast disorder

In the short term, 7.4% of the combined ILO group reported AEs and this was higher than the PBO (2.0%), HAL (1.7%), RIS (5.9%), and ZIP (1.3%) groups. Specifically, ejaculation failure, erectile dysfunction and retrograde ejaculation were more often reported in the combined ILO group. In the long term, the incidence was very low; ILO 10-16 mg/day 7.8% compared to HAL 4.4% and RIS 6.5%.

Respiratory, Thoracic and Mediastinal Disorder

Short term: 14.9% of the combined ILO group reported AEs and this was higher than PBO (7.8%) (MH=14.45, p<.001), RIS (9.2%) and HAL (10.2%) but similar to ZIP (13.3%). The ILO 20-24 mg/day group was higher (16.4%) than the ILO 10-16 mg/day group (13.7%). Nasal congestion, dyspnoea, nasal dryness and epistaxis were more frequently reported in the combined ILO group compared to the PBO. The frequency of reporting was slightly higher in Week 1 but there does not appear to be a duration-related pattern for ILO.

Respiratory AEs were more often considered drug-related in the ILO groups (ILO 10-16 mg/day 1.9% and ILO 20-24 mg/day 6.6%) and ZIP (4.7%) groups than in the PBO, HAL and RIS groups (3.3%, 1.0%, 0% and 1.0%, respectively). AEs considered more frequently drug-related in ILO groups, and in particular in the ILO 20-24 mg/day group, were dyspnoea and nasal congestion.

Serious adverse events (SAEs) and deaths

The ISS give the summary statistics for serious adverse events in short term PBO-controlled dataset and long term double-blind dataset. In the PBO-controlled dataset, 6.5% of combined ILO group had an SAE; this was lower than PBO (8.3%) (not significant), HAL and RIS (8.5% to7.5%, but not ZIP 1.3%) and the SAE frequency in the lower dose range was more than double that of the upper range (ILO 10-16 mg/day 9.1% and ILO 20-24 mg/day 4.1%). In the long term double blind studies, 18.1% of ILO 10-16 mg/day patients experienced a SAE and this rate was higher than that of RIS but similar to that of HAL (10.5%, and 16.1% respectively). The most commonly reported SAEs (>1%) were in the Psychiatric disorder SOC, and included schizophrenia 3.7%, suicidal ideation 1% and psychotic disorder 4.4%. SAEs in all SOCs occurring more frequently in ILO treated patients were: tachycardia, palpitations, psychotic disorder, suicidal ideation, suicide attempt, aggression, delusion, acute psychosis and insomnia. It should be noted that the incidence of most of the SAEs was <1%. In pooled open-label studies, 20.9% of all ILO treated patients reported a SAE (8.6% in Study 3101).

In the PBO-controlled group, 2.9% of the combined ILO group reported schizophrenia SAE and this can be compared to 3.2% in PBO, 0% in ZIP and RIS and 0.8% in HAL, with the ILO 10-16 mg/day group having a higher frequency than the ILO 20-24 mg/day group (4.3 versus 1.5%). In the long term, this was 5.5% in ILO 10-16 mg/day group compared to 2.4% in the HAL group and 3.3% in the RIS group. For Psychotic disorder, 1.6% of ILO treated patients reported a SAE and this was comparable to PBO (1.5%) and (ZIP 1.3%), higher than RIS (0.7%) but lower than HAL (2.5%). In longer term data, the ILO 10-16 mg/day group reported 4.4% a SAE which can be compared to 3.8% in the HAL group and 1.6% in the RIS group.

Drug-related SAEs

In Group 2, 0.7% of combined ILO group had a drug-related SAE, this was similar to ZIP but lower than all other groups and there was no dose-related difference across the ILO groups (0.6% and 0.8% in the ILO 10-16 mg/day and ILO 20-24 mg/day groups, respectively). In the longer term, 2.1% of SAEs were considered to be drug-related increased in the ILO 10-16 mg/day group to 1.6%, somewhat lower than HAL 3.3% and RIS 2.3%. Most drug-related SAEs were reported in only 1 patient.

Deaths

This section includes the entire extended dataset and extended dose range used. Over the course of the all ILO trials, 23 deaths occurred. Data were available from 19 of these (ILO 15, PBO 1, RIS 2, and HAL 4), the other 4 deaths occurred prior to randomisation. Thirteen (of the 19) deaths occurred in the Long term phase. There were 5 suicides and 3 ILO treated patients died of a cardiac event (all 3 of which were determined by investigators to be unrelated to study drug). One additional death occurred in the open-label phase of Study 3101 which was not included in the Integrated Safety Database.

AEs leading to death

ILO (n=3877): cardio-respiratory failure unknown 1, cardiac failure 1, pneumonia 1, struck by automobile 1, sudden cardiac arrest 2, sudden death 1, suicide 4, diabetes mellitus 1, pylorus occlusion 1, renal failure 1, septicaemia 1 and volvulus 1.

HAL (n=546): suicide 1

RIS (n=358): undetermined aetiology/natural 1

PBO (n=687): cardio-respiratory failure 1

Only one death was classified as suspected to be due to study medication by the investigator. In Study 3002, an Asian female patient aged 29 years in the ILO 10-16 mg/day group died suddenly. The patient had shown an S-T segment elevation in her ECG on study entry but was still enrolled. On study Day 166 chlorpheniramine (4 mg 3 times daily) and Actifed (triprolidine 2.5 mg and pseudoephedrine 60 mg, 3 times daily) were initiated for allergic rhinitis. On Day 170 the patient was found dead in the morning. The cause of death was listed as psychosis, however no autopsy was conducted and the exact cause of death is unknown. All other deaths were not considered related to study medications.

In Study 3101 (open label), one death occurred suddenly on study Day 65. Investigators were unable to assess the relationship of it to the study drug as the cause of death was not known; no death certificate was issued and an autopsy was not conducted.

Laboratory Findings

Laboratory values are evaluated in terms of changes from baseline values to both study endpoint and to worst recorded value. Clinically notable changes are defined as values outside the extended normal range (ENR); ENR equals the normal range± 15%. Normal ranges were specified in study protocols for all parameters analysed and were consistent across all studies.

Overall, ILO had no clinically meaningful effect on any haematology, biochemistry or urinalysis parameters.

Haematology

Among all haematological parameters examined intergroup differences[11] were only noted for haemoglobin and platelet count.

Haemoglobin: short term counts were statistically significantly lower in both ILO dose groups than PBO in mean change to baseline and mean change to endpoint. Counts were lower also comparators in both comparisons (no statistical tests undertaken). There were no dose-dependent changes observed. Long-term, the ILO 10-16 mg/day group was lower than HAL and RIS in change to worst value and lower than HAL in change to endpoint. Absolute values were low, and as there were no changes in red blood cells and haematocrit changes in haemoglobin values are unlikely to be clinically significant.

Platelets: short term mean changes from baseline to worst value and to endpoint were lower in both ILO dose groups than in the PBO and other comparator groups. The ILO 20-24 mg/day group had a somewhat greater change than the lower dose group in (change to worst value (-0.6 $10e^9$/L versus -0.3 $10e^9$/L; change to endpoint 5.5 $10e^9$/L versus 2.0 $10e^9$/L) In the long term studies, ILO 10-16 mg/day was lower than both HAL and RIS in change from baseline to endpoint and worst value.

For the majority of hematologic values percentage of patients who had a normal value at baseline and an abnormal value during treatment was 1% or less, and intergroup differences were observed for eosinophils, lymphocytes and monocytes. These were not considered clinically meaningful.

[11] Intergroup differences were determined using the following criteria:

- Mean change from baseline to worst value during treatment or mean change from baseline to endpoint in one treatment group was at least twice that in other group
- One of those treatment groups was ILO
- Mean change from baseline to worst value or the mean change from baseline to endpoint being compared had a value >= 1.

Clinical chemistry

Parameters assessed: liver function tests (alkaline phosphatase (ALP), bilirubin, aspartate aminotransferase (AST) alanine aminotransferase (ALT) and albumin), renal function anolytes (blood urea nitrogen (BUN) and creatine), metabolic function anolytes (cholesterol, glucose, and triglycerides) and electrolytes (chloride, carbon dioxide (CO_2), magnesium, potassium and sodium).

Liver and Renal function

Overall there were no clinically meaningful changes in liver function parameters in either short term or long term datasets. Where there were differences from PBO observed, absolute value changes were small and unlikely to be clinically meaningful.

In terms of renal function, there were some minimal changes in creatinine levels in some study groups; however these are unlikely to be clinically meaningful and overall ILO does not appear to have an effect on renal function.

Metabolic function

Anolytes assessed included cholesterol, creatine phosphokinase, globulin, glucose, high density lipoprotein (LDH) and low density lipoprotein (LDL), prolactin, triglycerides and thyroid stimulating hormone (THS). It should be noted that glucose concentration was not measured under fasting conditions in every study.

Prolactin

In PBO-controlled studies the ILO 10-16 mg/day group had an 11.2 ug/L decrease and the ILO 20-24 mg/day group had a 2.5 ug/L increase in prolactin from baseline to endpoint compared to a 40.9 ug/L decrease in the PBO group. These differences were not statistically significant in ANCOVA analysis. In the analysis of mean change to worst possible value, the pattern was similar (ILO 10-16 mg/day -2.2 ug/L, ILO 20-24 mg/day +2.4 ug/L, and PBO -41 ug/L). In the ANCOVA analysis there was no difference between either ILO dose group and PBO. Note, for both ANCOVA analyses there are very large SDs, very large ranges and CIs that cross zero, indicating some instability in the data. There were very large increases in the HAL and RIS groups, but not in the ZIP group, in the short (HAL 162.0, RIS 246.0, ZIP 2.1 ug/L) and long term (HAL 154.7, RIS 271.4 ug/L). In the long term, the ILO 10-16 mg/day group showed a slight decrease (11.2 ug/L). In open-label pooled studies, the mean change to baseline to endpoint in all ILO treated patients was -71.9 ug/L (-2.5ug/L in open label Study 3101).

In terms of clinically notable abnormalities, in the short term, the combined ILO group had a higher percentage of patients with values higher than the ENR than PBO (17.4% versus 4.8%) (ILO 10-16 mg/day 19.4% and ILO 20-24 mg/day 15.8%). These were much lower than HAL and RIS but not ZIP (73.1, 84.8, and 9.5%, respectively). In the longer term, the ILO 10-16 mg/day group remained lower than the HAL and RIS groups (19.8%, 68.9% and 84.9%, respectively).

Overall, ILO has a favourable prolactin response compared to PBO and active comparators known to have an effect on prolactin. According to the data presented, it does not cause a significant elevation of prolactin.

Other metabolic parameters

Table 20 below gives mean changes from baseline to endpoint, baseline to worst value and percentage of clinically notable abnormalities for a range of metabolic indicators in the short and long term datasets. However, there is insufficient data to make meaningful

comparisons for some parameters and groups. The proportion of each treatment group that was assayed for metabolic analytes varied considerably. For the Short term PBO-controlled studies, >87% of patients had values for cholesterol, glucose, lactose dehydrogenase (LDH) and triglycerides, but fewer than 10% of ILO patients had values for high-density lipoprotein, while only 3.7% of ILO 10-16 mg/day had values for low-density lipoprotein (ILO 20-24 mg/day 63%). Likewise in the longer term dataset, >90% of patients had data for triglycerides, glucose and cholesterol, 34% of ILO patients for LDH but only <2% for high or low-density lipoproteins. Where the data was available in only < 10% of a treatment group it has been omitted.

Table 20. Metabolic parameters mean changes from baseline and % outside ENR, short- and long term datasets.

	PBO	ILO 10-16 mg/d	ILO 20-24 mg/d	HAL	RIS	ZIP
Glucose						
Mean change to endpoint (nmol/L) Short-term (long-term)	0	0.5 (0.3)	0.7	0.8 (0.1)	0.1 (0.1)	0.5
Mean change to worst value (nmol/L) Short-term (long-term)	0.1	1.2 (0.8)	1.4	1.3 (0.5)	0.3 (0.2)	0.7
% above the ENR Short-term (long-term)	11.0%	22.9% (14.9%)	17.4%	21.4% (13.1%)	14.7% (15.8%)	9.9%
LDH						
Mean change to endpoint (U/L)	4.8	0.5	0.2	7.1	1.2	3.5
Mean change to worst value (U/L)	3.2	-1.8 (2.7)	-0.8	2.4 (5.8)	-0.8 (2.3)	2.5
% above the ENR	1.5%	2.2% (2.4%)**	0.5%	4.5%	1.5%	0
Triglycerides						
Mean change to endpoint (nmol/L)	-0.3	-0.3 (-0.2)	-0.1	-0.1 (0)	-0.3 (-0.4)	0.1
Mean change to worst value (nmol/L)	-0.3	-0.2 (0)	0.0	-0.1 (0.2)	-0.4 (-0.4)	0.2
% above the ENR	12.4%	14.0% (14.6%)	13.0%	16.1% (18.0%)	9.0% (10.8%)	17.6%
Cholesterol						
Mean change to endpoint (nmol/L)	-0.2	-0.1 (-0.1)	0.1	0.0 (0.0)	-0.1 (-0.1)	0.1
Mean change to worst value (nmol/L)	-0.1	-0.1 (-0.1)	0.2	0.2 (0.0)	0.0 (-0.1)	0.2
% above the ENR	3.3%	1.7% (6.5%)	10.1%	0.9% (8.6%)	0.7% (0.7%)	12.0%

**only had HDL data on 34% of long term sample.

There are few differences between treatment groups in mean changes from baseline to endpoint or worst value in both the short and long term datasets. There is a difference between ILO and PBO in % of glucose values outside the ENR. There does not appear to be any dose differences here for any measure except for % total cholesterol outside the ENR; it is substantially higher in the ILO 20-24 mg/day group than the other groups, including ILO 10-16 mg/day, with the exception of ZIP.

The lack of separation between active comparators and ILO raises some questions. RIS is known to have metabolic effects but in this data it has values intermediate between PBO and ILO (or lower for cholesterol). Given the very minimal numeric changes in metabolic

values in all treatment groups and that measurement was not made under fasting conditions in most studies, the robustness of ascertainment methods for metabolic measures and time of observation may have been inadequate to sufficiently characterise metabolic effects of Ilo.

Electrolytes

There were no intergroup differences between ILO and PBO in changes from baseline to endpoint or worst value for any electrolyte assessed.

Urinalysis

In short term data, the combined ILO group had higher percentage of patients with a change from baseline to worst value than PBO (and all other treatment groups) for epithelial cells (-0.9%) and urine glucose (2.7%), and in the extended dataset for calcium oxylate crystals (2.0%), squamous epithelial cells (0.9%) and urine glucose (2.0%). For urine glucose the two lower dose groups were higher than the ILO 20-24 mg/day group (3.3 and 3.1% versus 1.6%) in the PBO-controlled dataset, however by endpoint there was no discernible pattern. There were no other dose dependent patterns noted in the ILO groups for other analytes. In longer term data, percentages of patients with any calcium oxylate crystals were; PBO <1%, combined ILO group 3.5%, HAL 3.7%, RIS 0, ZIP 0. However, in Group 2 there was no difference between ILO (<1.0%) and the comparators (0-<1.0%). This suggests that there may be processing method differences for that analyte. The only clinically meaningful differences appear to be in urine glucose which suggests that ILO treatment may be associated with some degree of asymptomatic hyperglycaemia.

Vital signs

Parameters assessed included: supine pulse, 3 minute standing pulse, supine systolic blood pressure, 3 min standing systolic blood pressure, supine diastolic blood pressure and 3 minutes standing diastolic blood pressure.

Body Weight

In the short term PBO controlled dataset, overall change in weight (increase and decrease averaged) from baseline to endpoint wass greater for the combined ILO group (2.35 kg) than the PBO (-0.1 kg)group and there was a greater change in the ILO 20-24 mg/day group (2.7kg versus 2.0 kg); both groups were statistically significantly different from PBO. Active comparators also had less change than ILO: HAL -0,1kg, RIS 1.5 kg and ZIP 1.1 kg. In overall change (increase and decrease averaged) from baseline to worst possible value the same pattern is observed: ILO combined 2.6 kg (ILO 10-16 mg/day 2.2 kg, ILO 20-24 mg/day 2.9 kg) compared to PBO 0 k g. Again, both dose groups are statistically significantly different to PBO. In the long term dataset with respect to change from baseline to endpoint, ILO 10-16 mg/day was higher than comparators (2.6 kg versus HAL 0.8 kg and RIS 1.7 kg). A similar pattern was seen in change to worst possible value (ILO 10-16 mg/day 3.2 kg, HAL 0.9 kg and RIS 2.1kg). In the pooled open-label extension studies the overall change was 2.5 kg for ILO overall to endpoint, 3.1 kg for those who continued on ILO and 3.5 kg for both groups in change to worst value. In the open-label phase of Study 3101 (with a higher dose level) the results were similar, a 2.55 kg increase for ILO overall, with a 2.91 kg increase in those continuing on ILO.

Table 21. Weight change in short and long term datasets

	PBO	ILO 10-16 mg/d	ILO 20-24 mg/d	ILO combined	HAL	RIS	ZIP
Short Term							
Mean change to endpoint *(kg)*	-.01	2.0	2.7	2.35	-0.1	1.5	1.1
>7% increase	4.3%	12.1%	18.4%	15.3%	5.2%	11.9%	5.4%
Reported as an AE	0.7%	1.2%	9.5%	5.4%	0.0	2.6%	4.7%
Long-term double-blind							
Mean change to endpoint *(kg)*	-	2.6	-	-	0.8	1.7	-
>7% increase		28.7%			17.6%	14.2%	
Reported as an AE	-	2.7%	-	-			
Open-label							
Mean change to endpoint *(kg)*	-	2.5+	2.5*	2.5	-	-	-
>7% increase	-	33.7%+	37.7%*	35.7%	-	-	-
Reported as an AE							

(ISS 16.1.2, 16.1.3)

+ Pooled open-label studies dose range 4mg – 16 mg/d, median dosing 11mg/d

* Study 3101, flexible dosing 12 to 24 mg/d, median dosing 21 mg/d

Worst values increased

Examining weight increase only in the short term data the change from baseline to worst possible value was 3.76 kg and 4.09 kg in the ILO 10-16 and 20-24 mg/day groups, respectively, both being higher than PBO (2.44 kg). In the long term, this rose to 5.36 kg in the ILO 10-16 mg/day group, to 7.4 kg in ILO treated patients in open label studies, with the worst increase seen in those continuing on ILO (7.8 kg).

>7% increase

In the short term, 15.3% of the combined ILO group had a >7% increase in weight, with the proportion being higher in ILO 20-24 mg/day group (18.4% versus 12.1%). Both groups were higher than PBO (4.3%), HAL (5.2%) and ZIP (5.4%). The ILO 20-24 mg/day group was higher than RIS (11.9%). In the longer term, the proportion of the ILO 10-16 mg/day group with a >7% increase in weight increased to 28.7%. Of note, the ILO 4-8 mg/day group also had a substantial increase from short to long term (10.8% - 16.5%) which may indicate a dose-related response. The ILO 10-16 mg/day group was higher than both HAL 17.6% and RIS 14.2%. In pooled open-label studies, 33.7% or patients had a >7% weight increase, with the highest number being in those continuing on ILO (36.9%). In the open-label phase Study 3101, 37.7% of all patients had a >7% weight increase, with the higher being those continuing on ILO (47.7%).

Reported as AE

In the short term PBO controlled studies, weight increase was more frequent in both ILO groups, and much higher in ILO 20-24 mg/day (9.5%) than ILO 10-16 mg/day (1.2%), compared to PBO and HAL (0.7% and 0.0%, respectively). It was somewhat lower for the ILO 10-16 mg/day group but not the ILO 20-24 mg/day group compared to the RIS (2.6%) and ZIP (4.7%) groups. Weight increase was considered drug-related much more frequently in the ILO 20-24 mg/day group (8.4%), than in the PBO and ILO 10-16 mg/day groups (PBO 0.7%, ILO 10-16 mg/day 1.0%) and the HAL (0.0%), RIS (2.0%) and ZIP (4 .0%) groups. In the Long term dataset, the incidence of drug related weight increase was

more than double in ILO 10-16 mg/day (2.7%) group but it remained lower than the frequency in ILO 20-24 mg/day group in the short term phase.

Overall, ILO treated patients had an average acute weight increase between 2.1 – 2.7 kg which appeared to stabilise over time. The ILO 20-24 mg/day group had greater weight increase, a greater proportion of patients with a >7% increase in weight and reported more weight increase AEs than the lower ILO dose group. There is insufficient data available to assess if in the longer term weight continued to increase in patients on ILO 20-24 mg/day as it did moderately in the lower dose group.

Other Vital signs

Pulse rate (3 min standing only): in Short term data in Week 1, increased pulse rates were observed in both ILO groups and RIS for mean change from baseline, with ILO 20-24 mg/day dose group having a greater increase. By Week 2, the rates were declining, however, by study endpoint pulse rates were still higher than baseline in both ILO groups. In the longer term, from 6 weeks to 6 months, pulse rates had returned to baseline levels in both ILO dose groups (note there were fewer than 20 patients in the ILO 20-24 mg/day dose group with data for that period, so no conclusions can be drawn about that dose over the longer term).

In the short term, 29.2% of the combined ILO group had a clinically notable increase in pulse rate[12]. This was higher than PBO, HAL RIS and ZIP (6.7%, 17.8%, 21.9%, and 10.1%), with the higher ILO dose group having higher frequency than the lower dose group (33.8% versus 23.1%). In longer term data, there was little change from the short term data (ILO 10-16 mg/day 22.6%, HAL 11.2%, RIS 22.9%). In the open-label extension studies, rates declined to 8.7% for all ILO patients, although those who switched from PBO to ILO had more notable PR elevations (24.2%) than those continuing on ILO (6.9%). This may indicate longer term adaptation to initial pulse rate increases.

Blood pressure (3 min standing)

Systolic: Maximum negative change occurred for ILO at Week 5-6 and the mean values remained lower over the course of observation up to 12 months and beyond. In the Short term PBO-controlled dataset, the mean decrease from baseline to endpoint was greater in the ILO 10-16 mg/day (-4.8 mmHg) and ILO 20-24 mg/day groups (-4.8 mmHg) than in all the other comparator groups (-1.2 to +0.5). Over the long term, the pattern was unchanged for ILO 10-16 mg/day, HAL and RIS. In the short term, the combined ILO group also had greater mean change from baseline to worst value decreased; ILO 10-16 mg/day -19.3, ILO 20-24 mg/day -18, compared to PBO (-14.1), ZIP (-12.4), HAL (16.9) and RIS (-14.6). Systolic values were similar to or slightly lower than PBO for mean worst elevated values. In the open-label phase, at endpoint the HAL-ILO group had greatest mean change (-6.5 mmHg) compared to ILO-ILO (-4.9 mmHg).

The incidence of notably decrease[13] in systolic blood pressure (BP) in the combined ILO group in PBO-controlled dataset was 19.2% (ILO 10-16 mg/day 18.8%, ILO 20-24 mg/day 15.6%) and higher than that of the PBO (8.3%), RIS (11.3) and ZIP (8.1%) but similar to HAL (16.9%). This rose somewhat in the longer term for ILO 10-16 mg/day (23.3%) and for HAL (23.7%) but not for RIS (12.0%). For notably increased systolic BP, the ILO groups were slightly lower than PBO, HAL and RIS and comparable to ZIP in the PBO-controlled

[12] Clinically notably pulse rate events (defined as post baseline PR of >=120 bpm that increased by >=15 bpm, or post baseline PR of ± 50bpm that decreased by >=15bpm.)
[13] Defined as a post baseline systolic reading of ≥150 mmHg that increased by ≥10 mmHg, or a post baseline systolic reading of ≤90 that decreased by ≥10, or a post baseline diastolic reading of ≤65 that decreased by ≥10

dataset (PBO 19.4%, ILO 10-16 mg/day 18.8%, ILO 20-24 mg/day 17.6%, HAL 22.9%, RIS 22.3% and ZIP 18.8%)

Diastolic blood pressure

In the extended dataset, mean changes were worst at Week 4 in the combined ILO group (-5.1 mm HG), after which it returned gradually to baseline. However, at the endpoint of the PBO-controlled period values had not yet begun this decrease.

In PBO-controlled dataset, the mean change from baseline for decreased diastolic BP was greater in the ILO 10-16 mg/day and ILO 20-24 mg/day groups (-4.4 and -4.3, respectively) compared with PBO (-0.1), HAL (+0.9), RIS (-0.6) and ZIP (0.2). Likewise, the combined ILO group had greater mean change from baseline to worst value (ILO 10-16 mg/day -14.7, ILO 20-24 mg/day -14.7, PBO -11.1, HAL -11.6 RIS 13.8 and ZIP 10.3.). Diastolic values were comparable across treatment groups for mean worst elevated. In longer term for decreased BP, changes from baseline to endpoint and to worst value were largely the same as the short term. For decrease in diastolic BP, values outside the ENR were greater in the ILO groups than the PBO (ILO 10-16 mg/day 236 49.2%, ILO 20-24 mg/day 196 50.1%, and PBO 37.7%) as well as lower in active comparators (HAL 44.9%, RIS 40.2% and ZIP 28.2%). In the longer term, the proportion of ILO 10-16 mg/day group with decreased BP increased to 60%. HAL (49.7%) and RIS (41.2%) also showed a rise but not to the same extent as the ILO group. In the open label phase, the greatest initial decrease were in ILO-ILO patients, however mean values remained within the normal range at all observation time points.

Orthostatic Hypotension[14]

In the short term PBO controlled dataset, the incidence of both acute and sustained orthostatic hypotension, was higher in the combined ILO group than the PBO and some of the comparator groups (see Table 22) with a similar pattern in the longer term dataset.

Table 22. Frequency of acute and sustained orthostatic hypotension in short- and long term data.

	PBO	ILO 10-16 mg/d	ILO 20-24 mg/d	HAL	RIS	ZIP
Acute						
Short-term	7.6%	20.6%	12.0%	15.3%	12.0%	2.0%
Long-term double blind	-	20.3%	-	11.7%	13.3%	-
Open label	-	8.2%+	10.4*	-	-	-
Sustained						
Short-term	0	3.5%	1.8%	0.8%	0	0
Long-term double blind	-	2.9%	-	0.7%	0	-
Open label	-	0.8%+	1.2*	-	-	-

+ Pooled open-label studies dose range 4mg – 16 mg/d, median dosing 11 mg/d.
* Study 3101, flexible dosing 12 to 24 mg/d, median dosing 21 mg/d

Body temperature

There were no clinically significant changes in mean body temperature during any observation period for any treatment group.

Electrocardiographic Monitoring

Parameters assessed include: heart rate QTc, PR, QRS and RR intervals.

[14] Defined as a drop in systolic blood pressure of greater than 30 mmHg from supine to standing for 3 mins.

Heart Rate and RR

In the extended dataset, mean changes in heart rate at Week 1 were elevated in all treatment groups when compared to the PBO (PBO -0.2 beats per minute (bpm), ILO 10-16 mg/day 6.1 ILO 20-24 mg/day 9.1 RIS 8.7, HAL 0.8 and ZIP 3.4) and initial elevations diminished over time. All values remained within normal heart rate limits. At endpoint, ILO 20-24 mg/day was down to 4.1 (6 week endpoint) and by 12 months ILO 10-16 mg/day was -1.9, worst value down to. Mean changes to worst value tended to be elevated and were higher in the combined ILO 10-16 mg/day group long term 13.2, short term ILO 20-24 mg/day -13.5 ILO group (13.2 bpm) compared to PBO (6.3 bpm) but similar to the comparators (HAL 10.5, RIS 10.1 and ZIP 10.5 bpm). The worst values generally appeared in the early phases of treatment.

In the PBO-controlled data, there was slight dose difference in mean increase (ILO 20-24 mg/day 9.1 bpm, ILO 10-16 mg/day 7.2 bpm), at Week 1 which at study endpoint had declined but was still apparent (ILO 20-24 mg/day 4.1 bpm, ILO 10-16 mg/day 1.1 bpm). No dose differences were noted in mean change from baseline to worst possible value.

PR interval and QRS duration

There were only minor intergroup differences in the PR interval and QRS duration parameters.

QTc Interval

Prolongation of QT interval (QTc values of >500 ms and changes in QTc interval of ≥60 ms) may predict, or indicate, the development of medically significant cardiac events such as torsades de pointes. There is some evidence from the nonclinical studies that ILO may potentially affect cardiac conduction. In Purkinje fibres from male dogs there was a dose-dependent ILO prolongation of repolarisation, however, at the highest concentration tested (10 μM) there appeared to be a depression in the plateau phase of the action potential (Study 0120065). ILO also produced rapid, reversible blockage of hERG currents *in vitro* (Study 008167)

Clinical studies included in the ISS all included routine ECG and one study was specifically designed to examine the effect of ILO on QTc interval (ILO 2328). That study and supporting data from the ISS are described here.

All interval data was corrected, with the sponsor preferring Fridericia's formula (QTcF) as more accurate than the more widely used Bazett's (QTcB) formulae. QTcF numerical values are lower than QTcB so in the discussion that follows, where absolute value increases or decreases based on thresholds are presented, both sets of values are given.

In this section data from the lowest ILO dose group (ILO 4-8 mg/day) is included as Study 2328 used this dose, and it also may provide additional information about dose related effects.

ILO 522 2328: A randomised, open-label, multicentre, 5-arm, safety study evaluating the effect of oral ILO at doses of 8 mg bd, 12 mg bd, and 24 mg qd on at interval duration in the presence and absence of metabolic inhibition, relative to other antipsychotics (ziprasidone 80 mg bd, and quetiapine 375 mg bd, in the presence and absence of metabolic inhibition), in otherwise healthy patients diagnosed with schizophrenia or schizoaffective disorder.

Patients were randomly assigned to ILO 8, 12 mg/day bd, ILO 24 qd, ZIP 80 mg bd or quetiapine (QET) 375 mg bd. There were three treatment periods; Period 1 with no inhibiting agents, Period 2 with CYP2D6 and CYP3A4 inhibitors added to ILO and ZIP/QET, respectively, and Period 3 with CYP3A4 inhibitor added to ILO treatment. Changes in QTc were measured at t_{max}.

During Treatment Period 1 (no inhibiting agent), the mean change in QTcF from baseline to steady-state was similar for ILO 8 and 12 mg/day and ZIP (~9 -10 msec). ILO 24 mg/day was associated with the largest increase in QTcF from baseline (15.4±11.7 msec) whereas QET showed a lesser increase of 1.3±11.1 (Note: the large SD may indicate instability in the data). The difference in QTcF increase between the ILO dose groups was not statistically significant.

In Treatment Period 2, paroxetine (a CYP2D6 inhibitor) was added to the ILO treatment and it was associated with a modest increase in peak plasma concentrations of both ILO and its metabolite P88, and a corresponding modest increase in QTcF from Period 1 to Period 2. Ketoconazole, a CYP3A4 inhibitor, was added to the QET and ZIP treatment in this period and it resulted in a 300% increase in plasma concentration of QET with only modest increase in QTcF from Period 1 to 2. It also caused a modest increase in plasma concentration of ZIP with a moderate increase in QTcF.

In Treatment Period 3, ketoconazole was added to the ILO treatment. It caused peak plasma concentrations of ILO and P88 to substantially increase, with increases in QTcF across all 3 ILO treatment groups.

A statistically significant relationship between plasma concentration and QTc increase was observed for ILO in Period 3 and for P88 in Periods 2 and 3. There was no statistically significant relationship between plasma concentrations and QTc increase in the ZIP or QIT groups.

There appears to be a dose related increase in QTc interval with ILO treatment.

Adverse Events ILO 2328

No patient in any treatment arm had QTcF or QTcB value of >500 msec. Seven ILO patients had 8 instances when QTcF increased by >60 ms at t_{max}, however no adverse event occurred as a result of the QTc prolongation. Two ILO patients withdrew due to tachycardia. Both events resolved without sequelae and the effect appeared unrelated to drug plasma concentration since both occurred during titration phase of Period 1.

No instances of tachycardia were observed in any ILO patients receiving metabolic inhibitors during Periods 2 and 3 when plasma concentrations of ILO had doubled.

Both Studies 2328 and 3101 genotyped subsamples of patients to identify poor CYP2D6 metabolisers. Results showed that changes in QTcF interval were affected by metaboliser status; poor metabolisers having greater mean changes in QTcF from baseline to study endpoints.

Supporting PK studies:

The PK sub-study of Study VP 3101 examined effects of ILO over a plasma concentration range (C_{max}) of 1 ng/ml to ~47 ng/ml. QTc interval was prolonged between plasma concentrations of 10 ng/ml and 40 ng/ml but plateaued at 20 ng/ml above which there did not appear to be any further increase in QTc interval prolongation.

QTc in pooled ISD studies

In short term PBO-controlled data and the longer term dataset there is a trend toward dose related increases: ILO 4-8 mg/day 0.8%, 1%, ILO 10-16 mg/day 1.2%, 1.6%, ILO 20-24 mg/day 2.1%,2.3%, at Weeks 4 and 6, respectively. The increase in mean maximum values with dose was higher in the ILO 20-24 mg/day group (22.3 ms) than the other two doses (13.2 ms and 13.5 ms) but was similar to ZIP. All ILO doses were statistically

significantly higher than PBO. There was a similar pattern in mean change from baseline to endpoint. All mean maximum values remained within the upper limit of normal.

In the open-label dataset the mean maximum QTcF was 405.9 msec and this was similar to that reported from the double-blind phase and to that noted in patients switching from any comparator to Ilo. The mean change in those remaining on ILO was slightly higher; +29.33 ms. However, the mean change to endpoint in the combined ILO group was 15.3 ms and similar to that of the non-open label phases.

Outlier analysis

The proportions are higher when using QTcB, as the values are numerically higher and more patients therefore cross the thresholds. As this value is widely used the evaluator included it here. Table 23 gives QTcB and QTcF outlier analysis results.

Table 23. QTcB and QTcF outlier analysis

	PBO	ILO 4-8 mg/d	ILO 10-16 mg/d	ILO 20-24 mg/d	HAL	RIS	ZIP
QTcB							
>450	7.6%	10.5%	9.5% (9.9%)	24.5%	10.1% (7.7%)	6.3% (7.0%)	26.1%
>480	0.6%	0.5%	1.3% (1.2%)	3.5%	0.9% (0.6%)	0%	4.1%
>500	0	%	0.7% (0)	0	0	0	0
>15% change from baseline	3.1%	5.8%	5.8% (11.5%)	11.2%	0.9% (8.1%)	4.4% (5.9%)	7.4%
> 30 msec	19.7%	30.3%	28.3% (46.6%)	52.0%	23.9% (37.3%)	26.2% (29.2%)	47.3%
> 60 msec	2.8%	4.5%	4.3% (9.4%)	10.7%	0.9% (7.2%)	4.1% (5.2%)	6.8%
QTcF							
>450	1.1%	0.3%	1.6% (0.2%)	4.0%	1.8% (0.2%)	0.4% (0)	4.7%
>480	0	0	0.7%	0	0	0	%
>500	0	0	0	0	0	0	0
>15% change from baseline	1.1%	0.3%	2.2% (4.3%)	4.0%	0.9% (6.3%)	3.0% (3.7%)	4.1%
> 30 msec	11.1%	17.5%	19.1% (36.8%)	35.7%	15.6% (31.5%)	14.4% (17.7%)	31.8%
> 60 msec	0.9%	1.5%	1.3% (4.7%)	2.1%	0.9% (3.4%)	2.6% (2.6%)	3.4%

(ISS Tables 17.6.2 and 17.6.3)

In summary, there are greater increases in the highest dose group.

For both males and females in short term data, the ILO 20-24 mg/day (4.0%) had a higher percentage of patients with QTcF intervals ≥450 ms than PBO, HAL and RIS, but it was similar to that of ZIP (1.1%, 1.8%, 0.4% and 4.7% respectively). It was higher than the two lower ILO dose groups (ILO 4-8 mg/day 0.3%, ILO 10-16 mg/day 1.6). Females were higher in every treatment group except HAL. In the longer term, a higher percentage of females had QTcF interval ≥450 ms compared to males across all treatment groups.

In open label studies, 14.3% of ILO treated patients had QTcB > 450 ms, 1.2% > 480 ms and 0.3% > 500 ms. Some, 16.3% had an increase >15 %, 46.6% an increase > 30 ms and

14.2% an increase >60 ms. (QTcF: 0.4% ≥450 msec, 0% > 480 msec, 14.9% and increase of >15%, 48.4% >30 ms, and 11.2% >60 ms).

Other ECG abnormalities

In the short term safety database, 12.4% of the ILO 10-16 mg/day group and 34.1% of the ILO 20-24 mg/day group had ECG abnormalities. This can be compared to 15.5% of the PBO group (15.5%). Both groups were lower than ZIP (31.8%) but greater than RIS and HAL (10.3% and 8.3% respectively). ECG abnormalities that occurred at a rate more than twice that of the PBO in either the ILO 10-16 mg/day or the ILO 20-24 mg/day group were sinus tachycardia, T wave flat, T waves inverted, short PR, T Waves Biphasic, VPC, first degree AV block, t waves low – flat, atrial premature complexes and left anterior hemiblock. Those which occurred at higher rates in the ILO 20-24 mg/day group were sinus tachycardia, T wave inversions and first degree AV block. The pattern was similar in the long term dataset except that the incidence of ECG abnormalities in HAL had risen to (17.3%).

In the open-label pooled studies, approximately ~15% of all ILO treated patients had an ECG abnormality. This was similar to PBO in the double blind phase and also similar irrespective of the Phase 1 study drug taken. In the open-label phase of Study 3101, 27.7% of all ILO treated patients had ECG abnormalities.

Laboratory abnormalities with potential pro-arrhythmic effects

Frequencies of alterations in electrolyte levels (potassium, magnesium and calcium) were low and ILO did not induce any changes in electrolytes relevant to cardiac arrhythmias.

Safety in special populations

Pregnant and lactating women

There have been no adequate studies in pregnant women. Nonclinical studies in rats and rabbits show some developmental toxicity, early inter-uterine deaths and decreased fetal viability at very high does (equivalent to 20 times the maximum recommended human dose (MRHD)), but there was no evidence of tetrogenticity.

Nonclinical studies show ILO excreted in rat milk. There have been no studies in humans. The above are consistent with the draft PI recommending pregnant women not use ILO and that women taking ILO should not breastfeed.

Children and Adolescents

There have been no studies in children or adolescents under 18 years of age. Consequently the draft PI indicates this and does not recommend use in patients under 18 years.

Elderly Patients

The clinical efficacy and safety trials did not have sufficient numbers of patients with schizophrenia over the age 65 to observe age related effects. The draft PI states this and also includes the Class L labelling for Antipsychotics warnings of increased mortality risk in elderly patients with dementia-related psychosis and increased risk of cardiovascular (CV) adverse events, including stroke, in psychosis associated with Alzheimer's disease, indicating that ILO is not approved to treat these groups.

Gender

There were no meaningful gender differences between higher and lower dose groups with respect to percentage of AEs in short term PBO-controlled data. Both long and short term data of overall percentage of AEs reported show no gender differences in ILO treated patients when compared to PBO and comparator treated patients. Some gender differences were observed in QTc values. However, safety results are consistent with the draft PI statement that there is no effect of gender on AEs.

Safety related to drug-drug interactions and other interactions

ILO is metabolised primarily via CYP2D6 but the CYP3A4 pathway also plays a part. Safety for drug-drug interactions is drawn from PK interaction studies in healthy volunteers. Note that these studies used much lower ILO doses (3 mg maximum) than those being recommended for the treatment of patients with schizophrenia.

CYP2D6 substrates

Study ILO 0104 examined potential drug interactions in healthy volunteers genotyped as extensive metabolisers using dextromethorphan hydrobromide which is metabolised rapidly and extensively via the CYP2D6 pathway. There were no SAEs or deaths during the trial. In the overall study, 20 out of the 27 subjects reported AEs. The most common AEs thought to be related to study drug were dizziness, rhinitis, tachycardia, headache, nausea and vomiting. In the extensive metaboliser subgroup in the interaction phase of the study, there were more AEs reported after taking ILO alone (39 in 11 subjects) than after Ilo+DEX treatment (14 in 8 subjects). There were no differences between ILO only and Ilo+DEX in clinical laboratory values, vital signs or ECG findings.

Study ILO 0108 examined the effect of fluoxetine, a CYP2D6 inhibitor, in healthy volunteer extensive metabolisers. A total of 71 AEs were reported by 18 of the 23 study subjects; 42 occurred following 3 mg ILO alone, 17 following 20 mg fluoxetine alone and 11 following Ilo+Fluoxetine treatment. Some 62 of the 71 AEs were suspected to be study-related. All AEs were of mild or moderate severity. The most common AEs thought to be related to study medication were dizziness, nausea, nasal congestion and headache. The frequency of AEs was significantly higher in the ILO alone treated patients than in those given fluoxetine alone of Ilo+fluoxetine. There were small numbers of clinical laboratory values outside the normal range and most of these followed fluoxetine alone dosing.

CYP3A4 Substrates

Study ILO 0107 examined the effect of concomitant administration of ketoconazole (KET), a CYP3A4 inhibitor, in healthy volunteers. Subjects were given ILO 3 mg and KET 200 mg. A total of 127 AEs were reported by 18 of the 19 participants: 44 following 3 mg ILO alone and 83 in the ILO +KET group (3 of these occurred before ILO administration). Some 105 of the 127 AEs were suspected to be related to study drugs (33 ILO alone, 73 Ilo+KET). All AEs were of mild or moderate severity. AEs observed more frequently in the Ilo+KET group than following ILO alone treatment were: dizziness (ILO 47%, ILO + KET 68%), somnolence (ILO 21%, ILO + KET 53%), nausea (ILO 21%, ILO + KET 47%), scleral disorder (ILO 5% , ILO + KET 32%), and weakness (ILO 0 %, ILO + KET 16%). There were no differences between the ILO alone and Ilo+KET treatments in the number of laboratory abnormalities, vital signs or ECG readings. One subject discontinued after the ILO alone phase due to an ECG abnormality.

Anticholinergics

No formal safety analysis was undertaken with respect to concomitant anticholinergic use. Concomitant anticholinergic use was reported in ≤1% patients in any treatment group (PBO 1%, combined ILO group 1%, HAL 0.7%, RIS 1.0%, and ZIP 0.5%).

There was no overall increased incidence of AEs in patients using concomitant anticholinergic drugs compared to those who did not. The combined ILO group of patients who were using concomitant anticholinergic had a slightly increase in incidence of severe AEs, SAEs and permanent treatment discontinuations.

The combined ILO group of patients who were using concomitant anticholinergic drugs had slightly higher frequency of side effects commonly associated with anticholinergic use: dry mouth, headache, postural dizziness and nasal congestion, as well as higher (in at least 3 patients) abdominal pain/discomfort, asthma, back/extremity pain, cough, depression, diarrhoea, dyspepsia, EPS, exacerbation of schizophrenia, eye pain, fatigue, nausea, pain, suicidal ideation and toothache. However, these AEs occurred in a very small number of patients, insufficient to permit overall conclusions to be the drawn.

Discontinuation due to Adverse Events

In the short term PBO controlled studies, overall AEs led to permanent discontinuation in 12.7% of combined ILO group (ILO 10-16 mg/day 9.2% and ILO 20-24 mg/day 16.2%), with the lower dose being similar to PBO and lower than all other comparators The higher dose was higher than PBO and HAL, similar to RIS and lower than ZIP (PBO 11.0%, HAL 13.3%, RIS 17.9% and ZIP 25%). Most AEs led to treatment discontinuations in only 1 or two patients. AEs that led most frequently to treatment discontinuation (>0.2%) were nausea, dizziness, orthostatic hypotension, psychotic disorder and schizophrenia. Orthostatic hypotension led to discontinuation more frequently in the combined ILO group versus PBO and comparators (0.4% versus 0%), and schizophrenia more in ILO than HAL and ZIP, but not PBO or RIS (0%, 0%, 0.3% and 0.3% respectively). Over the longer term, 6.9% of AEs led to treatment discontinuation in the ILO 10-16 mg/day group. In the HAL and in RIS groups, 15.5% and 11.5% of AEs led to treatment discontinuation, respectively.

Post marketing experience

No systematic postmarketing data has been supplied. Two reports submitted to the FDA, for Quarters 2 and 3 of the year following approval (6 May to 6 August 2009 and 7 August to 6 November 2009, respectively) were included with the current submission. However, the drug had not yet been commercially available at that point so there was nothing to report. Subsequently, during the period from 6 November 2009 until 5 May 2010, a total of 4,960 prescriptions of ILO were sold in the USA. Aside from brief citations of selected postmarketing data in the risk management report, no additional postmarketing data were submitted with this application.

Evaluator's overall conclusions on clinical safety

Safety evaluations were comprehensive, with appropriate measures and frequency of assessments. No deaths were classified as related to study drug. One death was classified as possibly related but the relationship was unable to be determined. The incidence of serious adverse events was small. Treatment discontinuation due to AEs was low. In the data provided ILO does have greater frequency of AEs than PBO in a number of areas including: Nervous system, Cardiac, Renal, Reproductive and Respiratory SOC overall. QTc prolongation (multiple parameters), heart rate increase, pulse rate increase, hypotension and orthostatic hypotension, dizziness, sedation, somnolence, outside the extended range for glucose and prolactin and weight increase including >7% weight increase. Many of

these are typical to the class of drugs and comparisons with active agents provide more context as to the safety profile of ILO. In general, ILO has a favourable profile with respect to EPS and prolactin in the safety dataset and it shows few metabolic effects. However, there are several safety areas where it appears to have greater frequency of AEs than comparator agents included in the safety database, the most concerning being increase weight and cardiac problems, including QTc prolongation. A brief outline of both better and poorer performance with study comparators follows:

- ILO was better than HAL in overall incidence of AEs, long term drug-related AEs, short term nervous and musculoskeletal AEs, prolactin, akathisia, EPs, ESRS,
- ILO was better than RIS in the incidence of EPS, ESRS, tremor, akathisia, and prolactin.
- ILO was better than ZIP in the incidence of Nervous system AEs, akathisia AE, heart rate increase, gastro AEs, tremor, postural dizziness.

In terms of the profile of the overall class of drugs, ILO had no discernible impact on metabolic function. However, there is insufficient data to endorse such a conclusion. It is clear that there is a significant weight gain following ILO treatment which is greater than that of the comparators. It is therefore likely that over the long term metabolic effects would become apparent.

- ILO performed worse than HAL with respect to Cardiac AEs, heart rate, Respiratory AEs, overall weight increase AEs, 7% weight increase in long and short term, pulse rate, and QT parameters changes.
- ILO also performed worse than RIS in overall weight change and >7% weight increase in long and short term, long term severe AEs, Cardiac AEs, Respiratory AEs, Musculoskeletal AEs, heart rate increase and QTc (all parameters).
- ILO performed worse than ZIP in Cardiac AEs, weight increase and pulse rate. In general, the safety profile of ILO is consistent with this class of agents. It has advantages of a very low effect on EPS and prolactin. However, there are concerns regarding weight gain and its long term metabolic consequences. QTc prolongation effects are greater than the comparators except for ZIP and there may be an issue for those patients with an underlying cardiac condition.
- Dose response; The higher dose group had more AEs and laboratory and vital sign abnormalities than the lower dose group in most parameters of note, including: all AEs, drug-related AEs, severe AEs, Gastrointestinal AEs, Nervous system AEs, Respiratory AEs, Cardiac AEs, tachycardia and sinus tachycardia, dizziness, and sedation, hypotension and orthostatic hypotension, heart rate, QTc parameters, weight increase, >7% weight gain and pulse rate. For most of the AEs listed above, the ILO 20-24 mg/day group had a higher proportion than the ILO 10-16 mg/day group of AEs considered drug related.

Efficacy data seems to suggest that higher doses are more efficacious, and given that potentially fewer patients may discontinue due to EPS side effects, more patients may ultimately be receiving doses in this higher range. This is a cause for concern as there is no meaningful safety data available on this dose beyond 6 weeks (and limited data beyond 4 weeks). Weight gain is a concern. ILO at the doses being recommended did have greater increases in weight than comparators. There appeared to be a trend for weight gain to continue over time, which makes the lack of longer term data in the highest dose group of particular concern.

Overdose and potential for dependence

There is limited information on overdose but there have been no fatalities from overdose. Potential for dependence has not been determined.

Clinical Summary

This evaluation examined the data in a different grouping to that presented in the sponsor's Clinical Summary; specifically it did not include Study 2328 as part of the overall safety database as this was not a double-blind trial and was designed specifically to assess safety so bias in ascertainment is a risk. Also the evaluator generally did not include data from the lowest dose group (4-6 mg/day), as this dose has not shown efficacy and is not being recommended for use nor is approval sought for it in this application. Moreover, the evaluator restrict assessment of the highest dose group to Short term data rather than including it in Longer term datasets (the Safety Group 1 population used primarily in the sponsor's Clinical Summary). This is particularly important with respect to comparing the ILO dose group, as including the ILO 20-24 mg/day group in dose group comparison in the long term data misrepresents potential dose related patterns, as it compares up to 12 months of ILO 4-8 mg/day and ILO 10-16 mg/day group data to 6 weeks of ILO 20-24 mg/day data. It also, when there has been an increase over time in the lower dose groups, results in a combined ILO value that is lower than it might be were there long term data available on the highest dose. The evaluator believed that this approach to grouping the data is a more accurate representation of the data and more relevant to the parameters of this application.

Clinical Summary and Conclusions

Clinical aspects

Pharmacokinetics

The PK development program was comprehensive, well conducted and the PK properties of the parent compound and two major metabolites were well characterised. Effects of CYP2D6 and CYP3A4 inhibition and renal and hepatic impairment have been well characterised, as has the effect on PK parameters in individuals who are poor CYP2D6 metabolisers.

Direct comparisons between PK parameters in healthy volunteers and patients are not available, as the maximum tolerable dose of 3 mg/day in healthy volunteers is lower than the majority of doses used in PK studies in target populations, and is also lower than dose level sought in the application (12-24 mg/day).

Clinical efficacy

Based on the evaluator's view that the appropriate indication is the "treatment of Schizophrenia" rather than the "psychotic symptoms in patients with Schizophrenia", and EU guidelines[1] that evidence for such an indication should be ascertained from study populations that do not include schizoaffective disorder, there is evidence of efficacy across the 12-24 mg/day dose range for ILO in the treatment of schizophrenia.

The robustness of this evidence must be weighed in consideration of:

1. For the 24 mg/day dose there are two studies which provide positive evidence of efficacy in primary outcome analysis. However, efficacy for doses from 12 to 24 mg/day are supported by a single study only, and all secondary supporting efficacy data for those doses is drawn from studies that were negative for the combined schizophrenia and schizo-affective disorder populations.

2. The only trial designed for and conducted in schizophrenia only sample was only 4 weeks in duration.

Overall, although there is evidence of an improvement over PBO the effect sizes for ILO is modest, and although no formal head-to-head comparisons were conducted, currently marketed agents show greater numeric improvements in efficacy scale scores than Ilo.

For long term use, evidence of efficacy in maintenance is limited. Results of the pooled long term studies do adequately demonstrate the non-inferiority of ILO 4 – 16 mg/day to HAL as maintenance therapy.

There is no data on long term efficacy for doses above 16 mg/day to be used as maintenance therapy, nor with respect to other currently available agents.

Efficacy has not been investigated in paediatric or elderly populations.

Clinical safety

Patient Exposure

Short-term PBO-controlled: safety data is available for 874 patients in the recommended dose range of 12-24 mg/day ILO, 587 PBO, 118 HAL, 306 RIS and 150 ZIP patients for 4-6 weeks from 4 PBO controlled trials (71.31, 41.71, 8.13, 28.21, 9.17 patient years respectively).

Long-term (52 weeks) double-blind studies: safety data are available for 1425 patients in the 10-16 mg/day dose range, 546 HAL and 306 RIS patients (722.6, 261.6, 56.1). There is for practical purposes no safety data available for doses above 16 mg/day for this period.

Open-Label extension: safety data are available for 1042 ILO patients on a mean dose of 11 mg/day for up to 104 weeks from 7 pooled trials. Additional safety data is available from the open-label extension phase of Study 3101 (not included in the pooled data above) for 173 patients on mean dose 21 mg/day.

Adverse Events and Laboratory finding

In the data provided, ILO does have greater frequency of AEs than PBO in a number of SOCs: Nervous system, Cardiac, Renal, Reproductive and Respiratory SOC overall. Specific AEs and laboratory measures where ILO had a greater frequency than PBO include: QTc prolongation (multiple parameters), heart rate increase, pulse rate increase, hypotension and orthostatic hypotension, dizziness, sedation, somnolence, outside the extended range for glucose and prolactin, weight increase including >7% weight increase.

Many of the above are typical to the class of drugs and comparisons with active comparator agents better contextualise the safety profile of ILO:

ILO had a lower incidence than:

- HAL in overall AEs, long term drug-related AEs, short term Nervous system and Musculoskeletal AEs, prolactin, akathisia, EPS, ESRS[15] and Barnes Akathisia scale.
- RIS in EPS, ESRS, Barnes Akathisia scale, tremor, akathisia, prolactin.
- ZIP in Nervous system AEs, Barnes Akathisia scale, akathisia AE, heart rate increase, Gastrointestinal AEs, tremor and postural dizziness.

[15] ESRS=Extrapyramidal Symptoms Rating Scale.

ILO had a higher incidence than:

- HAL in heart rate, Cardiac AEs, respiratory AEs, overall weight increase AEs, 7% weight increase in long and short term, pulse rate and QTc prolongation.
- RIS in overall weight change and >7% weight increase in long and short term, long term severe AEs, Cardiac AEs, Respiratory AEs, Musculoskeletal AEs, heart rate increase and QTc prolongation.
- ZIP in cardiac AEs, weight increase and pulse rate.

Dose differences

The ILO 20-24 mg/day dose group had more AEs and laboratory assessment and vital sign abnormalities than the lower ILO 10-16 mg/day dose group in most parameters of note, including: all AEs, drug-related AEs, severe AEs, Gastrointestinal AEs, Nervous system AEs, Respiratory AEs, Cardiac AEs, tachycardia and sinus tachycardia, dizziness and sedation, hypotension and orthostatic hypotension, heart rate, QTc parameters, weight increase, >7% weight gain and pulse rate. For most of the AEs listed above a higher proportion were considered drug-related in the ILO 20-24 mg/day group than in the ILO 10-16 mg/day group.

Deaths and SAEs

No deaths were classified as related to study drug; one was classified as possibly related but the relationship was not determined and another was unable to be determined. The incidence of serious adverse events was low.

Discontinuation due to AEs

In the short term, AEs led to treatment discontinuation in 12.7% of the combined ILO group (ILO 10-16 mg/day 9.2% and ILO 20-24 mg/day 16.2%) compared to 11.0% of the PBO, 13.3% of the HAL, 17.9% of the RIS and 25% of the ZIP group. In the longer term, 6.9% of the ILO 10-16 mg/day group discontinued treatment due to AEs which can be compared to 15.5% in the HAL group and 11.5% in the RIS group.

Safety in special populations

Safety has not been established in paediatric or elderly patients.

Benefit risk assessment

Benefits

Note: The following pertains to schizophrenia only study samples.

Key Efficacy findings

Short term

Study 3101 demonstrates superiority of ILO over PBO for the 24 mg/day dose in patients with schizophrenia. After 4 weeks of treatment, ILO 24 mg/day patients showed a -4.92 (1.80) point greater mean decrease on the PANSS-T from baseline to endpoint than PBO (MMRM analysis 95% CI-8.47, -1.14, p=0.006).

Study 3005 demonstrates superiority over PBO for the 0-16 mg/day and 20-24 mg/day ILO dose ranges in patients with schizophrenia after 6 weeks of treatment. Patients given ILO 10-16 mg/day had a -3.1 point greater mean decrease on the BPRS from baseline to endpoint than PBO (ANCOVA analysis. 95% CI -5.9, -0.3, p=0.033). ILO 20-24 mg/day

patients had a -4.5 point greater mean decrease on the BPRS from baseline to endpoint than PBO (ANCOVA analysis. 95% CI -7.6, -1.3, p=0.005).

Long-term

Pooled analysis of three long term double-blind trials demonstrates non-inferiority of ILO to HAL with respect to survival until relapse.

Strength of evidence

Short-term

Both trials were randomised and double-blind with active comparators.

The relatively short duration of Study 3101 was considered to be a concern. EU guidelines recommend 6 week duration for short term PBO-controlled trials. However, a shorter duration would tend to bias toward underestimation of efficacy and given that the study did demonstrate greater improvement on ILO than on PBO over the 4 week period, the shorter time does not appear to have compromised it unduly.

Study 3005 had a mixed schizophrenia/schizoaffective population and when analysed according to protocol defined outcomes in the original population was an overall negative study (though secondary analyses did show positive results for the ILO 20-24 mg/day group). The efficacy results provided above are based on post hoc re-analysis in the schizophrenia only subgroup.

Both studies defined primary efficacy outcomes and instituted analytic designs to address the issue of multiple testing. While there were many secondary efficacy variables and subgroup analyses performed and cited in the application and product materials, the two studies show efficacy on the basis of those primary outcomes and thus provide valid evidence (albeit in an amended study population in post hoc re-analysis for Study 3005).

Long-term

The three studies pooled for analysis of long term maintenance effect were amended prior to study commencement to ensure an appropriate study population, that is, patients who had shown improvement in the short term phase of the trial and valid outcome measure, time to relapse, such that the resulting analysis was methodologically robust for demonstrating non-inferiority to HAL.

Comparison with other studies and products

Short-term efficacy

Data was available for only one study in a schizophrenia only population (Study 3101) to compare PANSS-T score reduction from baseline to endpoint. In that study there was a 12 point reduction in PANSS-T score. Compared to recently licenced antipsychotic agents, this change in scores is toward the lower end of the spectrum of effect size: Invega range from -15.0 to -23.3 and Serdolect -9.5 to -23.8 (MIMS data). Mean difference in change in PANSS-T scale scores from baseline to endpoint in ILO compared to PBO in the schizophrenia only study population of Study 3005 and in Study 3101 ranged between -3.1 to -4.9, again lower than Invega -7 to -17.9 (data not available for Serdolect).

Post hoc calculation of Cohen's d statistic indicates a small effect size for ILO 24 mg/day with respect to PBO in Study 3101 (d= 0.25102).

Over the clinical trial program as a whole, including studies with mixed schizophrenia/schizoaffective samples, effect sizes range from -9.5 to -14 points on the

PANSS-T, which are also toward the lower end of the range seen for Invega and Serdolect, as well as being lower than active comparator risperidone.

Risks

The key risks are weight gain, metabolic changes, QTc prolongation, orthostatic hypotension and long term safety in doses above 16 mg/day.

QTc prolongation

QTc prolongation was more frequent in ILO treated patients than in the PBO and active comparator groups. PK studies show that QTc prolongation was associated with plasma concentration of Ilo, and in Phase III studies QTc prolongation was dose related; the higher dose-range (ILO 20-24 mg/day) producing greater increases than the lower dose range (ILO 10-16 mg/day). The QTc prolongation caused by ILO was similar to ZIP but higher than HAL and RIS.

QTc prolongation >500 ms was only observed in ILO treated patients and not PBO or active comparator treated subjects. In the short term, 3 patients had a QTcB[16] score >500 ms (QTcF 0[17]). In the long term, two additional patients in the ILO 10-16 mg/day group had QTcB score >500 ms (QTcF0). No data were available for the ILO 20-24 mg/day group. In pooled open-label extension studies, 3 patients had >500 ms QTcB (QTcF 2).

There was a possible increase over time in the ILO 10-16 mg/day group in terms of >15% change from baseline, >30 ms increase and > 60 ms increase (5.8 to 11.5%, 28.3 to 46.6%, and 4.3 to 9.4%, respectively). The absence of long term data for doses above 16 mg/day is of concern given the dose related increase in QTc effects seen in the short term studies.

Weight Gain

In the short term 4-6 weeks, the average change in weight in the ILO group was an increase of 2.35 kg, with the upper dose range (ILO 20-24 mg/day) having a greater increase than the lower dose range (2.7 kg versus 2.0 kg). Both groups had a greater increase than PBO and the active comparator groups (PBO -0.1, HAL -0.1, RIS 1.5 and ZIP 1.1kg). The average increase in the highest dose group is comparable to olanzapine in short term studies; 2.6 kg (MIMS data). Some 18.4% of the ILO 20-24 mg/day group and 12.1 % of the ILO 10-16 mg/day group experienced a >7% increase in weight, which can be compared to 4.3% in the PBO, 5.2% in the HAL, 11.9% in the RIS and 5.4% in the ZIP groups.

In the long term data up to 52 weeks, the average weight change from baseline to endpoint in the ILO 10-16 mg/day group had increased to 2.6 kg, with no data available for doses above 16 mg/day. In that same dataset, both HAL and RIS had modest overall increases to 0.8 and 1.7 kg, respectively. Some 28.7% of the ILO 10-16 mg/day group had a >7% weight gain, with no data available for the ILO 20-24 mg/day group. This was higher than HAL and RIS (17.6 and 14.2%, respectively).

In open-label extension studies, the upper dose range in Study 3101 (with a median dose of 21 mg/day) shows that all ILO treated patients had a 2.5 kg mean change from baseline to endpoint, while the pooled dataset shows that for doses up to ILO 16 mg/day it was also

[16] The standard clinical correction to correct QT interval for heart rate is to use Bazett's formula, named after physiologist Henry Cuthbert Bazett, calculating the heart rate-corrected QT interval QTcB.

[17] QTcF: Heart rate-corrected QT interval using Fridericia's formula.

2.5 kg. The proportion of patients with a >7% weight change was 33.7% for doses up to ILO 16 mg/day and 37.7% for those on the median dose of 21 mg/day.

All longer term average weight increases in ILO treated patients are lower than olanzapine (5.6 kg MIMS data) but higher than the study comparators.

Table 24. Mean weight change and % of patients with >7% weight increase short- and long term data.

	PBO	ILO 10-16 mg/d	ILO 20-24 mg/d	ILO combined	HAL	RIS	ZIP
Short Term							
Mean change to endpoint *(kg)*	-.01	2.0	2.7	2.35	-0.1	1.5	1.1
>7% increase	4.3%	12.1%	18.4%	15.3%	5.2%	11.9%	5.4%
Long-term double-blind							
Mean change to endpoint *(kg)*	-	2.6	-	-	0.8	1.7	-
>7% increase	-	28.7%	-	-	17.6%	14.2%	-
Open-label							
Mean change to endpoint *(kg)*	-	2.5+	2.5*	2.5	-	-	-
>7% increase	-	33.7%+	37.7%*	35.7%	-	-	-

+ Pooled open-label studies dose range 4mg – 16 mg/d, median dosing 11mg/d
* Study 3101, flexible dosing 12 to 24 mg/d, median dosing 21 mg/d.

Metabolic function

For glucose, cholesterol and triglycerides levels the proportion of patients in the ILO 20-24 mg/day group with values outside the extended normal range (ENR) was higher than in the PBO group. The ILO 10-16 mg/day group also had a higher proportion of patients with values outside the ENR for glucose and triglycerides. The following table gives % of patients with values outside the ENR for the short and long term studies.

Table 25. Percentage of patients with metabolic changes above the ENR in short- and long term studies.

	PBO	ILO 10-16 mg/d	ILO 20-24 mg/d	HAL	RIS	ZIP
Glucose						
Short-term	11.0%	22.9%	17.4%	21.4%	14.7%	9.9%
Long-term	-	14.9%	-	13.1%	15.8%	-
Open label	-	11.3%+	9.2%*	-	-	-
Triglycerides						
Short-term	12.4%	14.0%	13.0%	16.1%	9.0%	17.6%
Long-term double blind	-	14.6%	-	18.0%	10.8%	-
Open label	-	9.8%+	10.7*	-	-	-
Cholesterol						
Short-term 4-6 weeks	3.3%	1.7%	10.1%	0.9%	0.7	12.0%
Long term to 52 weeks	-	6.5%	-	8.6%	0.7%	-
Open-label	-	11.3%+	8.3%*	-	-	-

+ Pooled open-label studies dose range 4mg – 16 mg/d, median dosing 11mg/d
* Study 3101, flexible dosing 12 to 24 mg/d, median dosing 21 mg/d. Note glucose was measured under fasting conditions.

RIS is known to have metabolic effects, however, in this dataset the RIS group are intermediate between PBO and ILO (or lower for cholesterol). Given the known metabolic effects of RIS, the acute weight gain observed with ILO, the small numeric changes noted in changes in metabolic values in all treatment groups (Table 25) and the fact that metabolic measures were not taken under fasting conditions in most studies, this data suggests that either the observation period was insufficient to ascertain metabolic changes related to short term weight increase in ILO or that ascertainment methods for metabolic measures were not sufficiently robust.

Orthostatic Hypotension

Patients treated with ILO 10-16 mg/day had higher acute and sustained orthostatic hypotension than all other treatment groups in the short and long term datasets but these differences are minor and of little clinical importance. Patients treated with ILO 20-24 mg/day had higher rates of acute orthostatic hypotension than PBO and ZIP but were similar to the other comparators (Table 25).

Quality of safety database

Over the course of development a large safety database was compiled, comprising 4 PBO-controlled double-blind short term trials, 4 long term double-blind trials, 7 open-label extension phase studies and one non-blinded short term safety trial designed specifically to examine QTc. This data set had a sample size sufficiently powered to adequately identify adverse effects. The documentation was extensive and detailed.

However, a serious limitation was the lack of safety data on doses above 16 mg/day for durations greater than 6 weeks, with the majority of data on the 24 mg/day dose being available for a 4 week period only. This is particularly concerning given the apparent dose-effect on AEs, such as weight gain and possibly QTc prolongation.

Balance

ILO doses from 12 – 20 mg/day have efficacy in symptom reduction in schizophrenia compared to PBO, although the potency of the therapeutic effect appears somewhat lower than currently available agents.

ILO doses from 10-16 mg/day are non-inferior to HAL as long term maintenance therapy. HAL is no longer widely used as first-line acute or maintenance therapy in Australia, however it has previously been considered an adequate maintenance therapy.

ILO has a lower incidence of EPS and akathisia than HAL, RIS and ZIP. EPS and akathisia characterise a number of antipsychotic agents and contribute to treatment discontinuation. The availability of an additional agent with a favourable safety profile with respect to EPS and akathisia will benefit patients.

ILO has no effect on prolactin which is adversely affected by some of the currently approved agents.

Weight gain was associated with ILO treatment and is a serious concern for schizophrenia patients who as a population have higher prevalence of overweight and associated metabolic abnormalities than the general population. The acute weight gain with ILO treatment was comparable to olanzapine which has well documented weight increase adverse effects. The weight increase that occurs following ILO treatment appears to plateau over the longer term at a level lower than olanzapine but higher than comparators in the safety dataset. However, data are incomplete, with insufficient data available on doses over 16 mg/day in the longer term to be able determine the long term effects of ILO with respect to weight increase.

Adverse metabolic effects are documented for some atypical antipsychotic agents, particularly olanzapine but also RIS. From the data presented it is unclear that metabolic effects have been adequately characterised, given the acute weight increase observed in ILO treated patients (which was comparable to that of olanzapine) and the lack of metabolic effects observed in RIS (which is known to have metabolic effects).

Overall, the QTc effects while of concern are similar to ZIP and the draft PI provides adequate information for physicians with respect to managing this risk. However, there is inadequate data available on doses above 16 mg/day in the longer term to determine long term safety.

Orthostatic hypotension is more pronounced with ILO than with PBO and for the lower ILO dose also more frequent than with the comparators. Orthostatic hypotension is a documented adverse effect of several other agents in this class and physicians are accustomed to managing it when adequately informed of the risk.

In general there is inadequate data to assess the overall long term safety profile of doses of ILO over 16 mg/day.

Of lesser concern but worth noting is that ILO dosing is somewhat more complex due to CYP2D6 interactions and poor metaboliser CYP2D6 status of some patients. Laboratory tests, while available to identify the latter, are not routinely used and such patients may initially experience higher than intended drug exposure levels.

Conclusions

The overall benefit risk balance of ILO was considered positive.

There is evidence of efficacy for ILO and it has a positive side effect profile with respect to EPS, akathisia, and prolactin. Weight gain, while not outside the range of currently available agents, was considered a concern. Some currently available agents also provide benefits with respect to EPS and prolactin. The lack of conclusive metabolic data and the lack of long term safety data on doses above 16 mg/day are concerning but the sponsor might be able address some of these issues. As far as the evaluator could ascertain, by carefully examining the data, although ILO has demonstrated efficacy is not likely to have high potency. On the other hand, all currently available atypical anti-psychotic drugs have considerable limitations. Many patients who suffer from schizophrenia prove to be either unresponsive or only partially responsive to available antipsychotics or experience intolerable side effects. There is an ongoing and critical need for a wider choice of anti-psychotics to be available for the clinician and it is for this reason the evaluator recommended the ACPM view this application favourably.

V. Pharmacovigilance Findings

Risk Management Plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR).

Safety Specification

The sponsor provided a summary of Ongoing Safety Concerns which are shown in Table 26.

Table 26. Ongoing Safety Concerns

Important identified risks	QTc prolongation Orthostatic hypotension and syncope Weight gain
Important potential risks	Increased mortality and cerebrovascular adverse events, including stroke, in elderly patients with dementia Hyperglycemia and diabetes mellitus Neuroleptic malignant syndrome Tardive dyskinesia Seizures Leukopenia, neutropenia and agranulocytosis Hyperprolactinemia Dysphagia Suicidality Priapism Cognitive and motor impairment Acute extrapyramidal symptoms
Identified interactions	Drugs that prolong the QTc interval Strong CYP3A4 inhibitors (e.g. ketoconazole) CYP2D6 inhibitors (e.g. fluoxetine, paroxetine)
Important missing information	Children and adolescents <18 years of age Elderly Pregnant and lactating women Patients with hepatic impairment

OPR reviewer comment:

Pending the evaluation of the clinical aspects of the safety specification, it was recommended to the Delegate that photosensitivity reactions be added to the list of Ongoing Safety Concerns as an important potential risk.

Pharmacovigilance Plan

The sponsor has proposed to undertake routine pharmacovigilance activities[18] for each of the Ongoing Safety Concerns. In addition, the sponsor has proposed to undertake a number of studies as additional pharmacovigilance activities for the Important missing

[18] Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

information 'Children and adolescents <18 years of age' and 'Patients with hepatic impairment'.

The proposed studies are:

- Children and adolescents <18 years of age
  - Paediatric pharmacokinetic and tolerability study: "An Open-Label Study to Assess the Safety, Tolerability, Pharmacokinetics, and Maximum Tolerated Steady-State Doses of ILO in Paediatric Patients with Schizophrenia."
  - Paediatric efficacy and safety study (exposure: 6-8 weeks): "A Randomised, Double-Blind, Parallel Group, Placebo-Controlled, Multi-Centre, Fixed Dose, 6-8 Week Study to Explore the Efficacy, Safety and Tolerability of ILO in Paediatrics with Acute Schizophrenia, Followed by an Open-Label 6 Month Extension."
  - Paediatric safety study (exposure: ≥ 6 months): "An Open-Label, Long-Term Safety and Tolerability Study of ILO in Paediatric Patients with Schizophrenia."
- Patients with hepatic impairment
  - Pharmacokinetic study in subjects with mild to moderate hepatic impairment: "An Open-Label, Single-Dose, Parallel-Group Study to Compare the Pharmacokinetics of ILO in Subjects with Mild or Moderate Hepatic Impairment with that in Matched Healthy Control Subjects."

Risk Minimisation Activities

The sponsor provided the following evaluation of the need for risk minimisation activities:

"Routine risk minimization activities are considered sufficient as all Important risks, Identified interactions and Missing information are addressed in the proposed PI."

As the sponsor only proposed to undertake routine risk minimisation activities, no risk minimisation plan was provided.

Summary of Recommendations

The OPR provided these recommendations in the context that the submitted RMP was supportive to the application; the implementation of a RMP satisfactory to the TGA was imposed as a condition of registration.

- There was no objection to the sponsor undertaking routine and additional pharmacovigilance activities as discussed above, however, further information was required to assess the usefulness of the paediatric studies as additional pharmacovigilance activities.
- The summaries of the proposed studies indicate that Australian patients will be included in all three of the studies; therefore, it is recommended to the Delegate that the sponsor be required to provide regular updates on each of these studies in a special section of the PSUR. In addition, as the studies are international studies, the sponsor should be requested to inform the TGA which of the international regulatory bodies will be providing the sponsor with the final approval for the studies.
- It was recommended to the Delegate that the sponsor confirm the current status of each of the studies in the pharmacovigilance plan and update the overview of study protocols for the pharmacovigilance plan and the summary of outstanding actions and milestones accordingly. In particular, the sponsor should confirm the status of the pharmacokinetic study in subjects with mild to moderate hepatic impairment; the RMP states that the submission of the final data is planned for 1 May 2011. If this is the

case, this study will not be considered as a pharmacovigilance activity as it will have already been finalised by the time the RMP is implemented in Australia. If this is the case, the RMP should be updated accordingly. Furthermore, the sponsor was requested to comment on whether it is their intention to submit the data from this study to the TGA for review, and if so, to provide a date by which they will they submit the data.

- The packaging in bottle rather than blister packs is unusual for a psychotropic medicine and presents as a risk for overdose. Psychotropic medicines are most often packaged in blister packs, as this makes it less likely for patients to intentionally overdose. It is recommended to the Delegate that the sponsor's comment on the decision to package the tablets in bottles rather than blister packs and to discuss what risk minimisation activities the sponsor will undertake to minimise the risk of intentional overdose.
- The sponsor's evaluation of the need for risk minimisation activities was not considered sufficient.
- As per the relevant guideline[19], it was recommended to the Delegate that the sponsor be required to discuss their conclusion regarding the need for risk minimisation activities and justify their decision to only undertake routine risk minimisation activities. Where appropriate, the sponsor was also asked to provide supporting evidence for their decision.
- In regard to the proposed routine risk minimisation activities, it was recommended to the Delegate that the sponsor makes several amendments to the PI.
- In regard to the proposed routine risk minimisation activities, it was recommended to the Delegate that the draft consumer medicine information document be revised to reflect any changes made to the PI.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There were no objections in respect of chemistry, manufacturing and controls to the registration of Fanapt tablets.

The quality evaluator noted that ILO contains no chiral centres and is obtained as a crystalline powder with no known polymorphs. There are three impurities with limits that exceed the ICH qualification threshold but the Medicines Toxicology Evaluation Section at the TGA advised that those limits have been satisfactorily qualified.

The tablets are uncoated, and unscored. Although the same excipients were used in all strengths, four slightly different granulation formulations were used to manufacture the seven strengths of tablet proposed for registration. The 1 mg and 2 mg tablets are unique formulations while the 4 mg and 8 mg tablets are direct scales and the 6, 10 and 12 mg tablets are direct scales.

[19] Part I, section 3.8 of Volume 9A - Guidelines on Pharmacovigilance for Medicinal Products for Human Use – of The Rules Governing Medicinal Products in the European Union.

The current submission was considered by the PSC at its 139th meeting in July 2011. The PSC endorsed issues raised by the TGA and these issues have now been satisfactorily resolved. The PSC requested analytical data for the three consecutive, full scale batches of the drug substance. These were provided. The PSC agreed that the sponsor's justifications for not conducting an absolute bioavailability study and for not conducting bioequivalence studies on all strengths of Fanapt were acceptable.

Nonclinical

There were no nonclinical objections to the registration of Fanapt tablets.

Safety pharmacology studies were not comprehensive, but *in vitro* tests showed inhibition of hERG currents by ILO (IC_{50} equivalent to 12.4 ng/mL at room temperature) but only minimally by the main human plasma metabolite. Canine Purkinje fibre action potential duration was significantly prolonged by ≥ 0.1μM ILO . Decreases in rat and dog blood pressures, associated with lower total peripheral resistance in dogs were observed in *in vivo* studies and probably related to antagonism of vascular α_1-adrenergic receptors.

In rats and dogs bioavailability was low with high first pass metabolism and clearance was primarily by faecal excretion. *In vitro* experiments suggested CYP2D6, and to a lesser extent CYP3A4, were important for ILO metabolism. Protein binding was 93% at 20 ng/mL in human plasma.

Repeat-dose toxicity studies were performed in rats and dogs with ILO exposures based on AUC that were >20 (rats) and >11 (dogs) fold that expected in humans with the maximum recommended dose. Besides clinical signs, impaired body weight gain and changes putatively ascribed to stress (lymphoid necrosis) and elevated prolactin (such as mammary gland activation) there were few significant effects of treatment. Rat mortalities were mainly associated with urogenital disease and also showed liver bile duct hyperplasia, possibly consequences of excretory overload. Nephrotoxicity and hepatotoxicity, including bile duct changes were also noted at a lethal dose in Han Wistar rats. Noteworthy oncogenic findings were increased mammary gland adenocarcinomas in female mice, but only with the low-dose, and increased pancreatic islet cell adenomas in rats. There was no evidence of teratogenicity with doses 2 fold that expected in humans given the maximum recommended dose.

Clinical

The clinical evaluator has recommended registration of Fanapt with an amended indication to reflect treatment of acute schizophrenia.

Pharmacology
The single dose PK studies in healthy volunteers were performed to a maximum dose of 3 mg due to the alpha adrenergic blocking effects of ILO . Steady state PK data to the maximum proposed dose were obtained from patients. ILO is well absorbed with C_{max} occurring within 2 - 4 hours. Absolute bioavailability has not been determined in humans.

ILO undergoes a significant first-pass effect, so that absolute bioavailability is estimated to be approximately 36% in CYP2D6 extensive metabolisers (EM) and 54% in CYP2D6 poor metabolisers (PM) (Sponsor's Clinical Overview). Absorption is not clinically significantly affected by food.

Protein binding is high at ~93%. ILO is metabolised by CYP 2D6 and CYP3A4. There are two major metabolites (P88 and P95). Clearance is ~ 47 to 102 L/h, with a volume of distribution (Vd) of approximately~ 1340-2800 L. The mean half-lives for ILO, P88 and P95 in CYP2D6 EM were 18, 26 and 23 hours, respectively. In PM the mean half-lives were 33, 37 and 31 hours, respectively. The ILO metabolite P95 represents 47.9% of the AUC of

ILO and its metabolites in plasma at steady-state for EM (25% for PM). The active metabolite P88 accounts for 19.5% and 34.0% of total plasma exposure in EM and PM, respectively. There was little difference in the amount of unchanged ILO excreted in urine in both EM and PM (0.45% and 0.7% of the given dose, respectively).

Dose proportionality at steady state was examined in 31 patients who had either schizophrenia or schizoaffective disorder. The kinetics were linear between 2 – 8 mg bd but with higher doses there was a loss of linearity, with higher than dose proportional exposure to ILO (AUC_T increased 7.7 fold between 2 mg bd and 12 mg bd).

There have been no studies in children, adolescents or in individuals aged > 65 years. The AUCs of ILO , P95 and P88 were 48.4% higher in women than men after adjustment for weight. A 2 fold increase in body weight resulted in a 13% reduction in average exposure. Severe renal failure (creatinine clearance (CrCL) < 30 mL/min) increased exposure to ILO by 23% (sponsor's Clinical Summary). The PK of ILO and its major metabolites was compared in patients with mild or moderate hepatic impairment (Child-Pugh from 5 to 9[20]) and healthy volunteers. Clearance and Vd of ILO in subjects with hepatic impairment were 9.8% and 17% lower, respectively. However, AUC was essentially the same. C_{max} and AUC for P88 were ~ 71% and 50% respectively, with renal clearance unchanged. The C_{max} and AUC_{0-t} for P95 were increased 19% and 20%, respectively, also without significant change in clearance. There was no difference in protein-binding.

The QT study compared the effects on QT interval of 8 mg bd, 12 mg bd and 24 mg once daily (od) ILO with daily doses of ziprasidone (80mg bd) and quetiapine (375 mg bd) at steady state. There were 3 treatment periods: Treatment Period 1 (dose titration and steady state without metabolic inhibition), Treatment Period 2 (addition of 1 metabolic inhibitor), and Treatment Period 3 (addition of a second metabolic inhibitor to the ILO groups). During Treatment Period 2, an inhibitor of the primary cytochrome P450 isoenzyme was added to each arm (ketoconazole, a CYP3A4 inhibitor for ziprasidone and quetiapine and paroxetine, a CYP2D6 inhibitor for ILO). During Treatment Period 3, only patients given ILO received ketoconazole in addition to paroxetine.

The primary QTc[21] analysis was the analysis of the primary variable (QTc change at the time of the peak plasma concentration (t_{max}) from baseline to steady state of Treatment Period 1) on the primary QTc population. Mean ΔQTcF was 8.5 ms for ILO 8 mg bd; 9.0 ms for ILO 12 mg bd; 15.4 ms for ILO 24 mg od; 9.6 ms for ziprasidone 80 mg bd and 1.3 ms for quetiapine 375 mg bd.

The addition of metabolic inhibitors in Treatment Period 2 increased the ΔQTcF to 17.5 ms for ILO 24 mg od; 15.9 ms for ziprasidone 80 mg bd; 11.6 ms for ILO 12 mg bd; 11.2 ms for ILO 8 mg bd and 2.6 ms for quetiapine 375 mg bd. With the addition of ketoconazole and paroxetine to ILO in Treatment Period 3 the mean ΔQTcF from baseline to steady state at t_{max} was 19.5 ms for ILO 24 mg od; 19.3 ms for ILO 12 mg bd; and 15.7 ms for ILO 8 mg bd.

Four patients in Treatment Period 3 experienced increases in QTcF of > 60 ms from baseline to steady state at t_{max}. One patient was in the ILO 8 mg bd group and the other three patients were in the ILO 12 mg bd group. No patients experienced QTc values (using any correction factor) of > 500 ms during this study. There appeared to be a dose-related increase in QTc with ILO . This was seen in the pooled short term studies where the mean

[20] The Child-Pugh score is used to assess the prognosis of chronic liver disease. The score employs five clinical measures of liver disease. Each measure is scored 1-3, with 3 indicating most severe derangement.

[21] QT_c: The QT interval is dependent on the heart rate (the faster the heart rate, the shorter the QT interval). To correct for changes in heart rate and thereby improve the detection of patients at increased risk of ventricular arrhythmia, a heart rate-corrected QT interval, *QTc,* is often calculated.

QTc increase in patients given ILO was 0.8% for patients given 4-8 mg/day, 1% for 10-16 mg/day and1.6% for 20-24 mg/day. The *Clinical Findings* section above describes outlier values of QTcB and QTcF for each of the ILO dose groups and placebo and active comparators. Increases in QTcF >60 ms were seen in 0.9% of patients given placebo, 1.5% given ILO 4-8 mg/day, 1.3% given ILO 10-16 mg/day and in 2.1% given ILO 20-24 mg/day. This compares with 0.9% given haloperidol, 2.6% given risperidone and 3.4% given ziprasidone.

Efficacy

The sponsor nominated four short term Phase III studies as pivotal: 3000, 3004, 3005, and 3101. These were designed with an initial, double blind phase followed by either a long term double-blind extension and/or an open-label long term extension. Efficacy was assessed in the initial, 6 week double-blind phase of each study (4 weeks in Study 3101).

Study 3101 was the only study nominated as pivotal that enrolled patients with schizophrenia only. It was placebo and active controlled with patients randomised to receive 12 mg bd ILO, 80 mg bd ziprasidone or placebo over 28 days. Patients with a history of psychotic symptoms that failed to improve following sufficient exposure to a therapeutic dose of any antipsychotic treatment over the last 2 years were excluded from study. The primary efficacy outcome was change from baseline to last scheduled observation in the PANSS-T. The primary analysis was of the modified ITT, MMRM with adjustment for centres and heterogeneity among centres.

A total of 593 patients were randomised. Mean baseline PANSS-T ranged from 90.32 to 92.67 across the 3 study arms. Some 381 (64.2%) patients completed the study. Withdrawal rates due to lack of effect were 20.6% for ILO, 23.5% for ziprasidone and 32.2% for placebo. Mean reduction in PANSS-T from baseline to study endpoint was -12.01 for ILO, -12.27 for ziprasidone and -7.08 for placebo. The difference between ILO and placebo was statistically significant (p= 0.006) for the primary analysis. The analysis of co variance (ANCOVA) (last observation carried forward (LOCF)) was also statistically significant however the ANCOVA OC was not. Secondary efficacy endpoint results were mixed with at least a trend towards better outcomes for patients given ILO rather than placebo for the majority of endpoints assessed.

The other studies nominated as pivotal enrolled a combination of patients with schizophrenia and schizoaffective disorder and a post hoc subgroup analysis of the primary efficacy endpoint was provided. Only 2 of the pivotal studies (3101 and 3004) demonstrated efficacy based on protocol defined outcomes in schizophrenia (3101) and schizophrenia or schizoaffective disorder (3004) in the dose range proposed by the sponsor. Studies 3000 and 3005 did not demonstrate statistically significant efficacy for all doses of ILO proposed. Table 27 below shows the pooled results for change from baseline to Week 6 in PANSS-T and BPRS for the subgroup with schizophrenia from Studies 3000, 3004, and 3005. Statistical analysis comparing each of the actives to placebo was performed with the primary analysis MMRM of the MITT population.

For the ILO 10-16 mg and 20-24 mg total daily dose groups both difference from placebo in change from baseline of PANSS-T and BPRS are statistically significant. Neither the 10-16 mg/day nor the 20-24 mg/day ILO dose group had as large a difference from placebo as either of the active comparators (haloperidol or risperidone) though no statistical analysis of the differences between active treatments was performed. Patients in both the ILO 10-16 mg/day and the ILO 20-24 mg/day groups showed statistically significantly larger mean reductions from baseline in PANSS-T and BPRS than placebo from Week 3 and statistical significance was maintained for the duration of the studies. ILO 4-8 mg/day did not separate from placebo at any timepoint for either parameter.

Table 27. Schizophrenia subgroup analysis. Studies 3000, 3004 and 3005. Table continued across two pages.

Analysis of Pooled Placebo-Controlled Data POSITIVE AND Negative Syndrome Scale (PANSS) Total Score Change from Baseline by Week and Diagnosis Mixed Model Repeated Measures (MMRM) Analysis Modified Intent-to-Treat Population (MITT)

Time Point	Placebo	ILO 4-8 mg/day	ILO 10-16 mg/day	ILO 20-24 mg/day	Haloperidol 15 mg/day	Risperidone 4-8 mg/day	Ziprasidone 160 mg/day
	N=(561)	N = (370)	N = (494)	N = (424)	N = (114)	N = (294)	N = (144)
Diagnosis: Schizophrenia							
Changes from Baseline to Week 6							
Estimate Mean Change (SE) [2]	- 9.6 (1.23)	-11.8 (1.47)	-14.9 (1.19)	-16.0 (1.70)	-19.9 (2.94)	-20.5 (1.46)	
95% CI	(-12.0, -7.2)	(-14.7, -8.9)	(-17.2, -12.6)	(-19.4, -12.7)	(-25.7, -14.2)	(-23.3, -17.6)	
Active-Placebo Difference [3]		-2.2	-5.3	-6.4	-10.3	-10.9	
95% CI		(-5.9, 1.6)	(-8.6, -1.9)	(-10.5, -2.3)	(-16.6, -4.0)	(-14.6, -7.2)	
P-Value [4]		0.2590	0.0019	0.0022	0.0013	<0.0001	
Brief Psychiatric Rating Scale (BPRS) Total Score							
Time Point	Placebo	ILO 4-8 mg/day	ILO 10-16 mg/day	ILO 20-24 mg/day	Haloperidol 15 mg/day	Risperidone 4-8 mg/day	Ziprasidone 160 mg/day
	N=(558)	N = (370)	N = (493)	N = (424)	N = (114)	N = (294)	N = (144)
Diagnosis: Schizophrenia							
Changes from Baseline to Week 6							
Estimate Mean Change (SE) [2]	- 6.3 (0.73)	-8.1 (0.87)	-9.9 (0.70)	-10.0 (1.02)	-12.3 (1.74)	-12.7 (0.86)	
95% CI	(-7.8, -4.9)	(-9.8, -6.4)	(-11.3, -8.5)	(-12.0, -8.0)	(-15.7, -8.9)	(-14.4, -11.0)	
Active-Placebo Difference [3]		-1.8	-3.5	-3.6	-5.9	-6.3	
95% CI		(-4.0, 0.4)	(-5.5, -1.6)	(-6.1, -1.2)	(-9.6, -2.2)	(-8.5, -4.2)	
P-Value [4]		0.1127	0.0004	0.0036	0.0017	<0.0001	

Notes:
- Baseline is defined as the last non-missing evaluation preceding the first dose of study medication.
- Included in the baseline summary are patients with both a baseline and at least one post baseline value.
- Adjusted baseline = Timepoint baseline – Mean of overall baseline values.
- SD = Standard Deviation, SE = Standard Error of the Mean, 95% CT = 95% Confidence Interval.
[1] MMRM model is adjusted for baseline; simple statistics provided for baseline
[2] Change is calculated as post – pre baseline value, so that a negative change indicates improvement.
[3] Active-Placebo Difference based on Adjusted Change Score from MMRM modelling.
[4] p-values (two-sided) from pair-wise chi-square contrast of each active treatment group to placebo.
- MMRM model includes no intercept term, dummy indicators for study and pooled centre, as well as the products of the dummy indicators for time with the adjusted baseline score and the dummy indicators for treatment

Maintenance of efficacy was assessed in 52 week extensions to Studies 3000 and 3004 and in 3 non inferiority studies (3001, 3002 and 3003). As noted by the clinical evaluator, the extensions to Studies 3000 and 3004 were not suitable for assessing longer term efficacy because the primary efficacy measure of change in scale scores from baseline to end of study does not effectively assess relapse or recurrence during the study period. In addition, at the end of the 52 week follow up period very few patients were available in either of these studies for assessment of the primary endpoint.

Studies 3001, 3002 and 3003 were of the same design and results were pooled. These were double-blind, 52 week prospective studies comparing maintenance of the antipsychotic effect of ILO 4-16 mg/day with haloperidol 5-20 mg/day in patients with schizophrenia or schizoaffective disorder over 46 weeks. Some 24-25% of study subjects had schizoaffective disorder (sponsor's Clinical Summary). Patients were included in the analysis population if they completed an initial double-blind phase of 6 weeks, showed a reduction from baseline in the PANSS-T of ≥ 20% at Weeks 4 and 6, had a CGI improvement score of < 4, took at least one dose of long term double blind study medication and had at least one efficacy assessment during the long term double blind phase. The primary outcome was survival time to first relapse.

These were non inferiority studies with a difference of no greater than 15% in the proportion of patients having a relapse considered not to be clinically important. Relapse was defined as any of the following:

- An increase (worsening) of the PANSS total score of at least 25%, including at least a 10 point increase;
- Discontinuation due to lack of efficacy;
- Aggravated psychosis with hospitalisation (adverse event);
- A 2-point increase (worsening) of the CGI-C score after Week 6.

Discontinuation rates were 30.5% for 3001, 51.5% for 3002 and 58% for 3003. In the pooled dataset the relapse rates were 156/359 (43.5%) for ILO and 47/114 (41.2%) for haloperidol. The between group difference of 1.03% (95%CI: 0.743, 1.428) is within the protocol specified -15%. Time to relapse was 89.8 days for ILO and 101.8 days for haloperidol. This study was not accepted as adequate to support a long term use indication for ILO in the USA because of its non inferiority design. In addition, the highest proposed doses 20-24 mg/day were not included in the assessment and patients with schizoaffective disorder were mixed with those with schizophrenia. A subgroup analysis of patients with schizophrenia was not included in the current submission.

Safety

A total of 874 patients with either schizophrenia or schizoaffective disorder were exposed to ILO in short term placebo controlled studies, 1425 patients were exposed in long term controlled studies (up to 52 weeks) and 1042 patients in open label studies. Some 624 patients have received treatment for between 6 and 12 months and 71 have received ILO for more than 12 months in controlled studies. No patients have received the highest proposed dose of 12 mg bd in long term controlled studies.

In the pooled short term studies, the discontinuation rates for patients given ILO were 22.1% for patients given10-16 mg/day and 28.2% for patients given 20-24 mg/day. These rates are slightly lower than the discontinuation rates in the active controls and approximately half the discontinuation rate in patients given placebo. The most commonly reported AEs considered treatment-related were: tachycardia; constipation; dry mouth; nausea, weight increase; dizziness; headache; sedation; and somnolence.

The areas of most concern appear to be QT prolongation, orthostatic hypotension and weight gain. All these events were dose-related. QT prolongation is somewhat less than occurs with ziprasidone. The addition of inhibitors of metabolism of ILO (ketoconazole and paroxetine) increases the mean QT increase to be similar to that of ziprasidone.

Orthostatic hypotension was reported as an adverse event in 4.9% of patients given 20-24 mg/day ILO and in 2.9% given 10-16mg/day. These events occurred after titration of the dose to limit this adverse effect.

In the short term studies the mean increase in weight in patients given 20-24 mg ILO for from 4 to 6 weeks was 2.7 kg with 18.4% of patients having an increase in weight of >7% body weight. Study 3101 had an open label extension where patients continued to receive flexibly dosed ILO with a mean dose of 21mg/day. Some 37.7% of these patients had body weight increases of >7%. Weight increases associated with ILO were considerably higher than those seen with haloperidol, risperidone or ziprasidone. Details of weight increases in comparators have been discussed by the clinical evaluator above.

Increases in prolactin were less than with haloperidone or risperidone and similar to those of ziprasidone. Extrapyramidal symptoms were assessed using an EPS rating scale and akathisia using the Barnes Akathisia Scale. Extrapyramidal symptoms in general and akathisia were less frequently observed in patients given ILO than active comparators. In the short term controlled studies 7.7% of patients given ILO had a worsening of akathisia. This was dose related, occurring in 5.9% of patients given 10-16 mg/day and 9.5% given 20-24 mg/day. This contrasts with increases in akathisia of 13.3% in patients given placebo, 18.9% given risperidone and 21.1% given ziprasidone. Less akathisia was also associated with ILO in the longer term studies, with worsening of akathisia occurring in 9.2%, 25% and 16.6% of patients given ILO, haloperidol and risperidone, respectively.

Changes in blood glucose and lipid profile were not well assessed due to the absence of testing under fasting conditions in the longer term studies. No large increases in glucose or LDH, triglycerides or cholesterol were apparent in the data submitted.

Twenty-three deaths were reported during the study program with data available for 19 cases (15 ILO). These are described under *Clinical Findings* above. Only one death was classified by the study investigator as suspected to be due to study medication. This was a sudden death in a 29 year old subject given ILO 10-16 mg/day. This patient had S-T segment elevation on study entry. During study chlorpheniramine, triprolidine and pseudoephedrine were given to these patients to manage allergic rhinitis. This patient was found dead 4 days after commencing this additional treatment.

Risk Management Plan

The evaluator of the RMP has negotiated a revised RMP and PI/ consumer medicine information (CMI) and there were no RMP issues that would preclude registration. The sponsor has disagreed with the recommended inclusion in the PI of the statement on akathisia that was recommended for inclusion in the PI of all atypical antipsychotic medicines by the Psychiatric Drug Expert Advisory Panel which reported to the TGA in December 2009.

The sponsor has planned PK and efficacy/ safety studies of ILO in children with schizophrenia, including a long term safety and tolerability study. A PK study in patients with hepatic impairment is also planned.

Risk-Benefit Analysis

Delegate Considerations

Pharmacology

There are several aspects to the pharmacology of ILO that limit its clinical utility. Firstly it has considerable alpha-adrenergic effects and so must be dose titrated over a week to achieve the highest recommended dose of 12 mg bd. Thus ILO will have a limited initial effect, and as a result it may not be suitable for the management of florid symptoms of acute psychosis in patients with schizophrenia.

The clinical utility of ILO is also limited by the need for dose reductions if given with strong inhibitors of CYP3A4 or CYP 2D6 and in patients who are CYP2D6 poor metabolisers. The dose of ILO also requires re-titratration after ceasing drug for more than 3 days. This may cause orthostatic hypotension in patients who are not fully compliant with their medication. There is also a risk that patients will not reduce their dose of ILO during treatment courses of medicines that interact with it to increase the concentration of ILO. That action is likely to cause an increase in dose related adverse events and in QT prolongation.

The QT interval was assessed at steady state and compared with the changes in QT interval with maximum recommended doses of ziprasidone and quetiapine when given to treat schizophrenia. ILO appears to have QT prolongation somewhat less than ziprasidone and more than quetiapine. There was assurance that the addition of metabolic inhibitors, shown to significantly increase exposure to ILO were not associated with sufficient QT prolongation to be associated with cardiac arrhythmias any more than currently available antipsychotic medication.

Efficacy

The Delegate considered that Study 3101 provides the pivotal evidence of efficacy of ILO in the treatment of acute schizophrenia. This study had a 4 week double blind treatment phase rather than the minimum period of 6 weeks recommended in the current *Note for Guidance on the Clinical Investigation of Medicinal Products in the Treatment of Schizophrenia*[22]*.*

Studies 3000, 3004, and 3005 are regarded as supportive because they enrolled patients with schizoaffective disorder as well as patients with schizophrenia and a *post hoc* subgroup analysis was required to determine efficacy in patients with acute schizophrenia. Only one of these three studies showed consistent efficacy above placebo for ILO in the treatment of schizophrenia. The pooled analysis of these studies showed a statistically significant improvement in PANSS-T that was greater than placebo but it was quite small and the clinical significance of the change is doubtful. The mean change in PANSS-T for patients given ILO was <20% from baseline. This ≥20% reduction in PANSS-T was taken as the cut-off for "response" for patients to be enrolled in the extension phase of these studies. Although there was no statistical comparison with active treatment groups in the post hoc efficacy analysis of pooled study results, both haloperidol and risperidone had larger mean reductions in PANSS-T than ILO. Although ziprasidone was not a comparator in the pooled analysis it also had greater mean reductions in PANSS-T than ILO in Study 3101.

The delay in onset of antipsychotic effect due to the requirement for dose titration on commencement of ILO is likely to limit use of this medication in the setting of acute schizophrenia.

[22] CPMP/EWP/559/95. http://www.tga.gov.au/pdf/euguide/ewp055995en.pdf

The long term efficacy and safety data of ILO in patients with schizophrenia was very limited. The pooled analysis to 52 weeks compared a mixed group of patients with schizophrenia or schizoaffective disorder who responded to either a comparator antipsychotic medication or ILO with at least a 20% reduction from baseline in PANSS-T score during the initial 6 weeks of double-blind treatment. There was no placebo comparison and no presentation of results for the subgroup with schizophrenia. There is a high placebo response rate for patients with schizophrenia so the absence of a placebo control arm in these studies is important.

The sponsor has proposed:

Treatment of psychotic symptoms in patients with schizophrenia

as the indication and has not specified the duration of treatment. The Delegate did not consider it acceptable to have a medication indicated for a symptom that occurs in the context of schizophrenia rather than for schizophrenia. Any indication that could be approved would have to be for the condition schizophrenia and not one of the symptoms of that condition. The absence of specification of the duration of treatment also present a difficulty as there are inadequate data on longer term use of ILO .

Safety

ILO appears to be associated with a reduced risk of hyperprolactinaemia and extrapyramidal side effects, including akathisia compared with the atypical antipsychotic medicines with which it was compared in the efficacy/ safety studies. It is associated with more weight gain than the comparator atypical antipsychotic medicines. Weight gain is dose related and increases with duration of exposure. The effect of ILO on glucose and lipid profile has not been adequately assessed in long term studies. Given the effect on weight it can reasonably be anticipated that ILO will have longer term adverse effects on glucose and lipid profiles. The effect of ILO on blood pressure was adequately managed by the titrated dose increase during the first week of treatment. The effect of ILO on blood pressure in clinical practise may not be as easily managed if patients become unreliable in taking their medication.

The sponsor has proposed that the dose of ILO be halved for patients with hepatic impairment. In the USA ILO is not recommended for these patients, however, the US PI states that a study in patients with hepatic impairment has not been conducted. Such a study was submitted for evaluation by the TGA. However, it was a single dose study with 2 mg of ILO whereas doses of up to 24 mg/day are proposed. An increase of approximately 50% in exposure to ILO was seen which is similar to that of women compared with men; however no dose adjustment has been proposed for women. As the PK are non linear with increasing dose it would be important to consider a multiple dose study at the proposed dose in patients with hepatic impairment prior to considering a dose adjustment for this patient group.

The draft PI has not specifically stated whether all patients should be tested for CYP2D6 metabolic status prior to determining the dose of ILO to be administered yet reducing the dose by 50% for this population is recommended in the draft dosing directions. This implies that routine testing to identify CYP2D6 poor metabolisers is required prior to finalising the dose of ILO.

Conclusion and recommendation

The Delegate proposed to reject Fanapt containing ILO 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12 mg as oral tablets for the

Treatment of psychotic symptoms in patients with schizophrenia

because:

- Psychotic symptoms are a component of schizophrenia whereas any indication for use of an atypical antipsychotic medication should reflect a clinical condition.

The Delegate considered a possible alternative indication of

Treatment of acute schizophrenia

However, the Delegate also rejected this indication because:

- The duration of assessment of efficacy was insufficient. The pivotal efficacy study for ILO in the treatment of acute schizophrenia had a 4 week double blind treatment period, however the TGA adopted guidelines recommend that treatment for acute schizophrenia be assessed over at least 6 weeks;
- The post hoc subgroup analyses of three studies of ILO that included patients with acute/ subacute schizophrenia treated over 6 weeks did not consistently demonstrate superior efficacy of ILO compared with placebo for the primary efficacy parameter. Only one of these three studies consistently showed a statistically significant difference between ILO and placebo for the primary efficacy outcome measure in the subgroup of patients with schizophrenia. While the pooled results from the three studies showed a statistically significant difference between ILO at the proposed doses and placebo, the clinical significance of that difference is uncertain.
- Given the delayed onset of action of ILO due to the need for dose titration additional treatment may be required for patients who have symptoms of acute schizophrenia of such severity that rapid onset of antipsychotic effect is desired. However, no such combinations of antipsychotic medications were examined in the clinical trial program.

An indication for:

Maintenance treatment in schizophrenia

This was also rejected because:

- Data on maintenance treatment was available only for a mixed group of patients with either schizophrenia or schizoaffective disorder who responded to treatment in short term studies. If acute treatment is not approved, it follows that maintenance treatment of responders to acute treatment who had schizophrenia cannot be approved. In any case, no subgroup analysis of patients who had schizophrenia and received maintenance treatment was provided.
- The lack of a placebo comparison in maintenance studies is particularly important given the high spontaneous improvement rate in patients with acute exacerbations of schizophrenia.

In addition, the following issues have not been adequately addressed in the current submission:

- The dose regimens for CYP2D6 poor metabolisers, patients with hepatic impairment and women have not been well justified. It is unclear if mandatory testing of CYP2D6 status is required and if so, how this would be implemented.
- The need to reduce the dose by 50% when ILO is given with strong CYP 3A4 inhibitors such as ketoconazole and clarithromycin or strong CYP 2D6 inhibitors such as fluoxetine or paroxetine and the need to re-titrate the dose during the course of

treatment of acute psychosis are likely to be quite difficult to implement unless the patient is hospitalised.

The advice of the ACPM was specifically requested regarding:

- Whether there is any indication that could reasonably be given for ILO given the limitations of the data;
- If approved, whether testing of CYP2D6 metabolic status should be mandatory for patients being considered for treatment with ILO , or if not mandatory, under what circumstances should it be required;
- If approved, should Fanapt be contraindicated in patients with hepatic impairment?

Response from Sponsor

Fanapt (ILO) is an atypical antipsychotic originally proposed to the TGA for the indication of:

Treatment of psychotic symptoms in patients with schizophrenia.

Although the sponsor believed that their proposed indication was scientifically justified, the sponsor agreed with the Delegate to change the proposed indication to

Treatment of schizophrenia.

This is consistent with the currently approved indication for ILO in the USA.

ILO has been shown to be effective in two short term studies in schizophrenia (one 4 week study and one 6 week study). Further, a pooled analysis of four short term studies (three 6 week and one 4 week in duration) confirm the efficacy of ILO at Weeks 4, 5 and 6 and at doses ranging from 12 mg to 24 mg per day. ILO has also been shown to be effective in a long term 52 week relapse prevention study. The magnitude of the treatment effect in all studies is clinically important and comparable efficacy to ziprasidone, haloperidol, and risperidone has been demonstrated, especially when comparisons account for the differences in titration schedules between different drugs. The safety profile of ILO is especially notable for its low risk of akathisia and other extrapyramidal movement disorders, along with a mild risk of weight gain similar to risperidone. The risk for prolactin elevation and, therefore, the attendant sexual side effects is much lower than that with risperidone and haloperidol. While ILO has a propensity to prolong the QT interval to a similar magnitude with that of ziprasidone, there is no evidence of this propensity leading to any cardiac arrhythmias. Importantly, the overall mortality rate of ILO is similar to placebo and generally lower than other approved antipsychotics.

The sponsor has prepared this document following receipt of the Delegate's report.

Short-Term Efficacy of ILO versus Placebo

Firstly, the Delegate raised a concern regarding the length of pivotal Study 3101. The Delegate writes,

"The duration of assessment of efficacy [for Study 3101] was insufficient."

The current *Note for Guidance on the Clinical Investigation of Medicinal Products in the Treatment of Schizophrenia* recommends a 6 week treatment period. The rationale for this recommendation was to decrease the risk of having a false negative study due to a shorter treatment time and was further reinforced in the most recent draft *Guideline on clinical investigation of medicinal products in the treatment of schizophrenia* released by the EMA in February 2011:

"The preferred design for demonstrating short term efficacy is a 6 week clinical trial. This is because so far for classical antipsychotics, a reasonable stability of effect has been observed as well as some effect on negative symptoms, often only after 6 weeks of treatment. Shorter study duration (e.g. 4 weeks) could also be considered, especially for drugs with a similar profile to existing antipsychotic drugs, although the latter carries the risk of negative results if maximal therapeutic effect is not obtained after 4 weeks."

Therefore, Study 3101, which established efficacy as early as 4 weeks of treatment, serves as a strong and even more clinically relevant pivotal study to support approval.

Second, the Delegate wrote,

"Studies 3000, 3004, and 3005 are regarded as [only] supportive because they enrolled patients with schizoaffective disorder as well as patients with schizophrenia and a post hoc subgroup analysis was required to determine efficacy in patients with acute schizophrenia."

Most approvals of currently-marketed antipsychotics were derived from programs that contained a mixture of schizophrenia and schizoaffective patients, as the debate around diagnostic categories between these disorders continues. In Study 3005, an analysis limited to the schizophrenia population (78% of total randomised) was strongly positive for both doses examined and consistent with the finding in Study 3101.

Third, the Delegate wrote,

"While the pooled results from the three studies showed a statistically significant difference between ILO at the proposed doses and placebo, the clinical significance of that difference is uncertain."

The magnitude of the treatment effect is clinically meaningful and comparable to other approved antipsychotics when properly adjusted. This is addressed in the *Comparative Efficacy* section below.

Fourth, the Delegate raised the concern that only two of the pivotal short term studies demonstrated efficacy. It is well known that, even for drugs that are known to be effective for the treatment of schizophrenia, on average one out of three short term placebo controlled trials will not show separation from placebo. A compilation by Dr. Thomas Laughren of all schizophrenia studies submitted to the FDA psychiatry review division highlights this observation.[23] Given the fact that ILO:

1. showed similar efficacy to haloperidol in the short term phases of the three active-controlled studies (Studies 3001, 3002, and 3003),
2. demonstrated non inferiority in the long term maintenance study described later in this document, and
3. demonstrated efficacy in two placebo controlled short term studies, the efficacy of ILO has been convincingly demonstrated.

In conclusion, the short term efficacy of ILO versus placebo in the treatment of schizophrenia has been established in two well designed studies and the magnitude of the demonstrated effect is clinically meaningful and the number of positive over negative studies is well within the expected for currently available antipsychotics.

[23] Laughren, T. P. 2001. The scientific and ethical basis for placebo-controlled trials in depression and schizophrenia: an FDA perspective. *Eur.Psychiatry* 16:418-423.

Comparative Efficacy of ILO versus Ziprasidone, Risperidone, and Haloperidol in Short-Term Studies

First, the Delegate incorrectly wrote

"*…ziprasidone also had greater mean reductions in PANSS-T than ILO in Study 3101.*"

This is not true as ILO achieved **-12.01** points reduction on the PANNS scale versus **-12.27** points for ziprasidone. No expert in the field would consider these effect sizes to be different.

Second**,** in the studies of which risperidone served as the positive control, ILO and risperidone achieve similar effect sizes, when adjusting for the different titration schedules. Specifically, the target dose of ILO was reached in 5-7 days, while the therapeutic dose of risperidone was achieved in 2 days. The sponsor performed a sensitivity analysis of the relative efficacy of the treatments among the 75% of patients who remained in the study for at least 2 weeks. Results of this analysis confirm that among patients treated with ILO 10 mg/day or more who remained on study drug for more than two weeks, antipsychotic effectiveness was similar for ILO and risperidone (in Study 3005, mean change from baseline at endpoint in the 18 item BRPS for ILO 12-16 mg/day = **-11.3**, ILO 20-24 mg/day = **-12.0**, and risperidone 4-8 mg/day = **-12.5**).

Third, the Delegate wrote

"*Neither the 10-16 mg/day nor the 20-24 mg/day dose group had a large difference from placebo as either of the active comparators (haloperidol or risperidone) though no statistical analysis of the differences between active treatments was performed.*"

Here, the Delegate implies that firm conclusions about comparative efficacy can be drawn from short term placebo controlled trials that include an active comparator. In fact, conclusions about comparative efficacy cannot be made with any degree of confidence from such studies. Reliable and valid methods for comparing the performance of active agents in short term placebo-controlled trials (PCTs) have not been established. This is particularly true in the setting of short term placebo controlled schizophrenia trials, where dropout rates typically average about 50%. Kemmler and colleagues have described the problems with obtaining unbiased estimates of treatment effect in such trials:

"High dropout rates entail the important problem of biased estimation of treatment effects. In particular, if attrition rates are as high as in the PCTs studied herein and elsewhere, with values approaching or exceeding 50%, the amount of bias may be considerable and may lead to erroneous conclusions…Even if more sophisticated methods of missing value replacement…are used, biased estimation of treatment differences remains a problem because all of these methods rely on hypothetical assumptions regarding the nature of the dropout process." [24]

With different forces driving the pattern of dropout for different drugs, estimating the ***relative*** treatment effects between those drugs becomes an even more difficult task. It has been recognised that dropouts due to early lack of efficacy are a feature of placebo controlled clinical trials, mainly because the treating investigators carry the concern that patients have been assigned to placebo. In clinical practice, early dropouts due to lack of efficacy are rare while patients are closely monitored in the acute setting. The sponsor discussed earlier that correctly accounting for titration differences allows for a more proper comparative analysis of two agents. Based on the above findings, comparative

[24] Kemmler, G., M. Hummer, C. Widschwendter, and W. W. Fleischhacker. 2005. Dropout rates in placebo-controlled and active-control clinical trials of antipsychotic drugs: a meta-analysis. *Arch Gen.Psychiatry* 62:1305-1312.

efficacy conclusions from active controlled studies without placebo arms should be more valid. To this point, ILO was equally effective as haloperidol in the short term phases of Studies 3001, 3002 and 3003, as well as the long term maintenance study. Nonetheless, ILO was also shown to be comparable to ziprasidone and to risperidone once accounting for titration differences.

Long-Term Maintenance of Effect of ILO /Comparative Efficacy of ILO versus Haloperidol

The Delegate wrote,

"The long term efficacy… was very limited. There was no placebo comparison…There is a high placebo response rate for patients with schizophrenia so the absence of a placebo control arm in these studies is important."

The sponsor did not agree with this assertion. In the community at large, the ethics of placebo withdrawal studies in stably treated schizophrenia patients is increasingly being questioned, just as long term treatment of schizophrenia patients with placebo has been questioned in the past. In addition, the value of such controversial studies are increasingly being questioned in light of the fact that no atypical antipsychotic that has shown to be effective in short term studies has yet to show lack of efficacy in long term studies. Responding to these criticisms, the most recent draft guideline on clinical investigation of medicinal products in the treatment of schizophrenia released by the European Medicines Agency (EMA) allows for non inferiority designs as valid and ethical study designs to support long term efficacy:

"*To demonstrate maintenance of effect, several study designs are possible:* ***parallel design*** *(with placebo and/****or active comparator****) or randomised withdrawal design. Extension studies may provide evidence of maintenance of efficacy as long as they stay double blind. A parallel trial using active comparator is the first possibility. When the objective is to show non-inferiority, the active control should be a product with a well documented efficacy in the maintenance of treatment effect in schizophrenia. Due to the natural course of the disease, the duration of such a trial should be 12 months and the assay sensitivity should be fully substantiated."*

The long term maintenance study for ILO fulfils the above requirements. The sponsor acknowledged that they did not include the schizophrenia only subgroup analysis in the original submission. The sponsor has recently performed this analysis for the submission that has been validated and is being reviewed by the EMA, the sponsor reported that non inferiority is maintained for the subgroup of patients with schizophrenia. The results are: relapse rates for ILO and haloperidol were 42.7 and 39.6, respectively, with the between group difference of 1.07% (95% CI: 0.750, 1.510).

An additional concern raised by the Delegate was,
"*the highest proposed doses 20-24 mg/day were not included in the assessment.*"

As discussed in the submission, the dose most often used in the long term studies was 12 mg/day with very little use of the 16 mg/day dose. While the open label extension data from Study 3101, which allowed long term use of 24 mg/day, revealed no significant tolerability issues, the sponsor felt that the 20-24 mg/day dose was needed for long term use and have recommended doses ≤16 mg/day for long term treatment in the proposed PI.

Need for Titration

The Delegate wrote

"…it has considerable alpha-adrenergic effects and so must be dosed titrated over a week to achieve the highest recommended dose of 12 mg bd. Thus, ILO will have a limited effect, and as a result it may not be suitable for the management of florid symptoms of acute psychosis in patients with schizophrenia."

The sponsor has already evaluated and demonstrated efficacy of ILO among patients with acute and florid symptoms of schizophrenia in Studies 3005 and 3101. Other highly effective agents such as quetiapine have a similar titration requirement and yet are considered effective for the management of florid symptoms of acute schizophrenia. It is well understood by treating clinicians that the full significant therapeutic effect should not be expected during the titration phase of an antipsychotic and supplementing with additional pharmacological options is normal practice. Therefore, there should be no additional safety risks inherently linked to an antipsychotic, like ILO , that may have a slow response in the initial days of treatment.

The Delegate also wrote

"*The dose of ILO also requires re-titration After ceasing drug for more than 3 days. This may cause orthostatic hypotension in patients who are not fully compliant with their medication*."

Lack of compliance is largely driven by tolerability issues experienced by the patient. For the patient who is non compliant because of akathisia or EPS, ILO , with its placebo like akathisia and EPS profile, should allow for better compliance. While no two patients are the same, alternatives to existing therapies are needed to address non compliance due to akathisia and EPS. Also, a titration pack has been specifically designed and provided in order to facilitate correct and well tolerated short titration.

Safety Profile

The Delegate raised some issues regarding the safety profile of ILO . The Delegate suggested that there is inadequate long term safety data for ILO because the database contains a mixed group of patients with schizophrenia or schizoaffective disorder and does not have long term placebo exposures as a reference. The sponsor disagreed with this assertion. *A priori*, there is nothing inherently different between a patient with schizophrenia versus one with schizoaffective disorder that should make one believe that the adverse event profile of ILO would be different between these two patient populations. In the clinical trial database, a total of 1210 patients received >6 months ILO treatment, with 700 of those receiving >12 months treatment. These numbers provide ample information to discern the long term safety of ILO. Additional data that should provide reassurance for the safety profile of ILO comes from the USA postmarketing data. In the 20 months that ILO has been available in the USA (through August 2011), an estimated 122,467 ILO prescriptions have been filled according to the IMS National Prescription Audit database. Assuming each prescription is for a 1 month supply, this correlates to approximately 10,066 treatment years. Post marketing safety surveillance in the USA is consistent with the safety profile of ILO described in the proposed PI or Consumer Medicine Information.

Addressing the well characterised effect on the QT interval, the Delegate stated;

"*There was assurance that the addition of metabolic inhibitors, shown to significantly increase exposure to ILO were not associated with sufficient QT prolongation to be associated with cardiac arrhythmias any more than currently available antipsychotic medication*."

The sponsor agreed with this conclusion.

Dose Adjustments

The Delegate raised three concerns regarding dose adjustments recommended for ILO.
Firstly, "*The need to reduce the dose by 50% when ILO is given with strong CYP 3A4 inhibitors…or strong CYP 2D6 inhibitors…are likely to be quite difficult to implement unless the patient is hospitalised*."

Dosage adjustments occur in clinics every day outside of the hospital setting. It is unrealistic to think that a physician could not easily write a prescription for a reduced dose of ILO if they co prescribe a CYP2D6 or 3A4 inhibitor. Furthermore, this situation is by no means unique to ILO. Abilify (aripiprazole) is a commonly used antipsychotic worldwide, including Australia. The Australian PI for Abilify (v4.0) recommends almost identical dose adjustments to those being recommended for ILO :

"Aripiprazole is metabolized by multiple pathways primarily involving the CYP2D6 and CYP3A4 enzymes. In clinical studies with healthy subjects, potent inhibitors of CYP2D6 (quinidine) and 3A4 (ketoconazole) decreased oral clearance of aripiprazole by 52% and 38%, respectively…When concomitant administration of quinidine or ketoconazole with aripiprazole occurs, the aripiprazole dose should be halved. When the inhibitor is withdrawn from the combination therapy, the aripiprazole dose should then be increased."

Similarly, for Abilify, the US PI and EMA Summary of Product Characteristics (SmPC) both recommend dose adjustments for known poor metabolisers (PM), yet neither have language requiring mandatory testing:

"Dosing recommendation in patients who are classified as CYP2D6 poor metabolisers (PM). The aripiprazole dose in PM patients should initially be reduced to one-half (50%) of the usual dose and then adjusted to achieve a favorable clinical response."

Therefore, nothing novel regarding dose adjustment of ILO has been proposed and, consistent with other approved medications, there should be no requirement for mandatory CYP2D6 testing to identify PMs.

Secondly, the Delegate raised the concern about whether dosage adjustments should be recommended for women. The sponsor acknowledged that the PK-PD analysis indicates on average that women experience 48% higher exposures than men, however, the practical importance of this finding is uncertain, as there is no evidence that women have more tolerability or safety problems than men when receiving recommended doses of ILO. Therefore, the sponsor did not feel that specific dose adjustment recommendations for women are warranted.

Thirdly, the Delegate's letter raises the question of whether ILO should be contraindicated in patients with hepatic impairment. A second hepatic impairment study is currently being performed. Until the results of this second study are available, the sponsor agreed that patients with hepatic impairment should not take ILO.

Conclusions

The sponsor felt that this response had adequately addressed all of the Delegate's concerns, allowing for the conclusion that ILO is a well characterised safe and effective treatment for patients with schizophrenia. Further, the sponsor agreed with the sentiment expressed in the TGA Clinical Evaluation Report:

"The overall benefit risk balance of ILO is positive [and]…all currently available atypical anti-psychotics have considerable limitations. Many patients who suffer from schizophrenia prove

to be either unresponsive or only partially responsive to available antipsychotics or experience intolerable side effects. There is an ongoing and critical need for a wider choice of anti-psychotics to be available for the clinician and it is for this reason the evaluator recommend the committee view this application favourably."

Advisory Committee Considerations

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM considered this product to have a negative benefit-risk profile for the proposed indication, for the following reasons:

- Efficacy in the treatment of acute exacerbations of schizophrenia has not been adequately demonstrated. There was one pivotal study in patients with acute exacerbation of schizophrenia; however, it was of insufficient duration to provide sufficient evidence of efficacy. The Committee does not accept the sponsor's claim that 4 weeks assessment is adequate to determine response in acute exacerbation of schizophrenia and notes this is not consistent with recommendations in the TGA's adopted EU guideline.
- There was insufficient evidence of maintenance of efficacy in patients with schizophrenia.
- The side effect profile of this product, particularly in regard to orthostatic hypotension, is of concern. Orthostatic hypotension commonly requires careful dose titration and management. This safety risk, when combined with likely limited compliance by many patients with schizophrenia has not been adequately assessed.
- There is inadequate long term safety data across the therapeutic dose range in the indicated population.
- The risk of concomitant or consecutive use of drugs known to be potent inhibitors and stimulators of the CYP2D6 pathway has not been adequately investigated.
- There was inadequate investigation into dosing in patients with reduced hepatic capacity in view of the 70% change in clearance in patients with moderate hepatic impairment. This presents significant risk for the proposed patient population.

Outcome

Based on a review of quality, safety and efficacy, TGA rejected the registration of Fanapt (iloperidone) 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12 mg oral tablets for the indication of:

The treatment of psychotic symptoms in patients with schizophrenia.

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