9 November 2017
EMA/844865/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Fanaptum

International non-proprietary name: iloperidone

Procedure No. EMEA/H/C/004149/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

5-HT_{2A}	serotonin 2A receptor
5-HT_{2C}	serotonin 2C receptor
ADME	absorption, distribution, metabolism, and excretion
ADO	adverse event related dropouts
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate transaminase
AUC	area under the curve
$AUC_{0-\infty}$	area under the curve from time zero to time infinity
AUC_{0-t}	area under the curve from time zero to the last measurable sampling time
BA	bioavailability
BE	bioequivalence
b.i.d.	bis in die / twice a day
BL	baseline
BMI	body mass index
BOCF	baseline observation carried forward
BPRS	brief psychiatric rating scale
C_{avg}	Average concentration at steady state, computed by the area under the concentration-time curve in a fixed dosing interval divided by the length of the dosing interval
C_{max}	maximum plasma concentration
CDSS	Calgary Depression Scale for Schizophrenia
CGI	clinical global impression
CGI-C	clinical global impression of change
CGI-I	clinical global impression of improvement
CGI-S	clinical global impression of severity
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL	clearance
CMH test	Cochran-Mantel-Haenszel test
CNS	central nervous system
CNTF	ciliary neurotrophic factor
Cp	plasma concentration
CPZ	chlorpromazine
CR	controlled release
CRO	contract research organisation
CT	computed tomography
CV	coefficient of variation
CYP	cytochrome P450 enzymes
D_2	dopamine receptor 2
DBRP	double blind randomised phase
ECG	electrocardiogram
EEG	electroencephalogram
EM	extensive CYP2D6 metabolizers
EMA	European Medicines Agency
EPS	extrapyramidal symptoms
ESRS	Extrapyramidal symptom rating scale
FAS	full analysis set
FMF	final marketing formulation
FMF-C	final marketing formulation capsules
FMF-T	final marketing formulation tablet
CGP	good clinical practice
h	hour
HAL	haloperidol
HPLC	high performance liquid chromatography
HMR	Hoechst-Marion-Roussell
iDMC	independent data monitoring committee

ILO	iloperidone
IR	immediate release
ISE	integrated summary of efficacy
ISS	integrated summary of safety
ITT	intention to treat
IV	intravenous
LOCF	last observation carried forward
LC-MS	liquid chromatography-mass spectrometry
MAA	marketing authorisation application
MITT	modified intention to treat
MMRS	mixed-model repeated measures
MRI	magnetic resonance imaging
MS	mass spectrometry
NE	norepinephrine receptor
OC	observed cases
PANSS	positive and negative syndrome scale
PANSS-GP	positive and negative syndrome scale – general psychopathology subscale
PANSS-N	positive and negative syndrome scale – negative symptom subscale
PANSS-P	positive and negative syndrome scale – positive symptom subscale
PANSS-T	positive and negative syndrome scale, total score
PBO	placebo
PD	pharmacodynamics
PI	product information
PK	pharmacokinetic
PM	poor CYP2D6 metabolizers
PPS	per protocol set
q.d.	once a day
QT	time between the start of the Q wave and the end of the T wave in the heart's electrical cycle
QTc	corrected QT interval
QTcF	corrected QT interval Fridericia's
RIS	risperidone
SAE	serious adverse event
SD	standard deviation
SE	standard error
SOC	system organ classes
ss	steady state
t.i.d.	three times a day
t_{max}	time to reach Cmax
$t_{½}$	half-life
TEAE	treatment emergent adverse event
ZIP	ziprasidone

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Vanda Pharmaceuticals Ltd. submitted on 4 December 2015 an application for marketing authorisation to the European Medicines Agency (EMA) for Fanaptum, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 22 January 2015.

The applicant applied for the following indication:

Fanaptum is indicated for the treatment of schizophrenia in adults.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/71/2011 on the granting of a product-specific waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance iloperidone contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 23 March 1999 and 21 September 2000. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Hanne Lomholt Larsen

Co-Rapporteur: Alexandre Moreau

- The application was received by the EMA on 4 December 2015.
- The procedure started on 31 December 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 21 March 2016. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 21 March 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 4 April 2016.
- During the meeting on 14 April 2016, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the meeting on 28 April 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 December 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 31 January 2017.
- During the PRAC meeting on 9 February 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 23 February 2017, the CHMP agreed on a list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 18 April 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 4 May 2017.
- During a meeting of an ad hoc expert group on 5 May 2017, experts were convened to address questions raised by the CHMP. The CHMP considered the views of the expert group as presented in the minutes of this meeting.
- During the CHMP meeting on 17 May 2017, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the CHMP meeting on 18 May 2017, the CHMP agreed on a 2nd list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 29 June 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the 2nd List of Outstanding Issues to all CHMP members on 5 July 2017.
- During the meeting on 20 July 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a marketing authorisation to Fanaptum on 20 July 2017.

1.3. Steps taken for the re-examination procedure

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: John Joseph Borg Co-Rapporteur: Greg Markey

- The applicant submitted written notice to the EMA on 27 July 2017 to request a re-examination of Fanaptum CHMP opinion of 20 July 2017.
- During its meeting on 14 September 2017, the CHMP appointed John Joseph Borg as Rapporteur and Greg Markey as Co-Rapporteur.
- The applicant submitted the detailed grounds for the re-examination on 26 September 2017 (Appendix 2 of the Final Opinion). The re-examination procedure started on 27 September 2017.
- The rapporteur's re-examination assessment report was circulated to all CHMP members on 11 October 2017. The co-rapporteur's assessment report was circulated to all CHMP members on 13 October 2017. The PRAC rapporteur's re-examination assessment report was circulated to all PRAC members on 11 October 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's detailed grounds for re-examination to all CHMP members on 5 November 2017.
- During a meeting of the Ad-Hoc Expert Group on Fanaptum on 30 October 2017, experts were convened to consider the grounds for re-examination. The CHMP considered the views of the Expert group as presented in the minutes of this meeting.
- During the CHMP meeting on 7 November 2017, the detailed grounds for re-examination were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 9 November 2017, the CHMP, in the light of the scientific data available and the scientific discussion within the Committee, re-examined its initial opinion and in its final opinion concluded that the application did not satisfy the criteria for authorisation and did not recommend the granting of the marketing authorisation.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Claimed indication: Fanaptum is indicated for the treatment of schizophrenia in adults.

2.1.2. Epidemiology

Schizophrenia is a psychiatric disorder that affects approximately 1% of the world-wide and the EU population.

2.1.3. Clinical presentation, diagnosis

It is characterized by the presence of positive symptoms (such as hallucinations and delusions) and negative symptoms (e.g. apathy, blunted affect and social withdrawal), as well as impairment of cognitive functions and mood symptoms. The disease is chronic and significantly debilitating on both the social and occupational functioning of patients. The disease is also associated with an increased mortality. More than 10% of patients with schizophrenia complete suicide in their lifetime. In addition, lifestyle factors (smoking, substance abuse, unhealthy food) contribute to the increased mortality. While significant advances have been made over the last fifty years, the pharmacological treatments available are merely symptomatic and mainly target the positive symptoms. A significant unmet medical need remains.

2.1.4. Management

Medicines in use for the treatment of Schizophrenia are usually classified into first generation (or typical) and second-generation (or atypical) antipsychotics.

First-generation (or typical) antipsychotics such as chlorpromazine and haloperidol, reduce positive symptoms of psychosis by acting as antagonists on the D2 receptors of the mesolimbic pathway. The same effect on D2 receptors on the nigrostriatal pathway is believed to be associated with the high incidence of Extrapyramidal symptoms observed with these drugs. An upregulation of the same receptors on this pathway is believed to be the cause of the long-term development of tardive dyskinesia.

The class of second-generation (atypical) antipsychotics includes clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, asenapine, lurasidone and sertindole. The medicines in this class share the characteristic of binding both the dopamine and serotonin receptors, but they are also different in the combination of receptors they bind and their affinity for those receptors. These differences result in unique clinical profiles, especially on aspects of their safety profiles. The NIMH-sponsored CATIE study demonstrated a significant unmet medical need, despite the use of these compounds, with approximately 75% of the patients discontinuing their medication within an 18-month period for both lack of efficacy and side effects (Lieberman et al, 2005). The most significant side effects of the available antipsychotics are weight gain, diabetes, dyslipidaemia, extrapyramidal symptoms, akathisia, prolactin elevation, sedation, QTc prolongation, and in the case of clozapine, agranulocytosis.

About the product

Iloperidone is a piperidinyl benzisoxazole derivative developed for treatment of the symptoms of schizophrenia. It acts as antagonist at dopaminergic, serotonergic and adrenergic receptors having affinity to dopaminergic D_2 and D_3 receptors, serotonergic 5-HT_{1a} and 5-HT_{2a}, and adrenergic α_1 and α_{2c} receptors.

The pharmacological profile of iloperidone is consistent with one of a second-generation antipsychotic.

The Applicant claims that the antipsychotic activity will be associated with a reduced liability for extrapyramidal symptoms.

Iloperidone is formulated as tablets of 1, 2, 4, 6, 8, 10 and 12 mg each. The recommended starting dose is 1 mg b.i.d, which must be slowly titrated to the target dose range of 6-12 mg b.i.d. to avoid orthostatic hypotension due to the α-adrenergic inhibitory activity of the compound.

In May 2009, iloperidone tablets (Fanapt) have been approved for the treatment of schizophrenia in adults by FDA. Due to its propensity to cause QT-prolonging, the product has been licensed as second line treatment.

Type of Application and aspects on development

The applicant applied for the following indication: Fanaptum is indicated for the treatment of schizophrenia in adults. The legal basis for this application refers to: Article 8.3 of Directive 2001/83/EC - complete and independent application.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as tablets containing 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg or 12 mg of iloperidone as active substance.

Other ingredients are: lactose monohydrate, microcrystalline cellulose, hypromellose, crospovidone XL (Type A), magnesium stearate, and colloidal anhydrous silica.

The proposed packaging consists of full aluminium (polyamide/aluminium/polyvinyl chloride foil – aluminium lid) blisters placed into a paperboard cards and sealed (dose titration cards) for treatment initiation; or HDPE bottles with a child-resistant polypropylene closure containing an aluminium foil heat induction seal, and a silica gel desiccant, for dose maintenance.

2.2.2. Active Substance

General information

The chemical name of iloperidone is 1-[4-[3-[4-(6-fluoro-1,2-benzoxazol-3-yl)piperidin-1-yl]propoxy]-3-methoxyphenyl]ethanone corresponding to the molecular formula $C_{24}H_{27}FN_2O_4$ and has a relative molecular mass 426.48 and has the following structure:

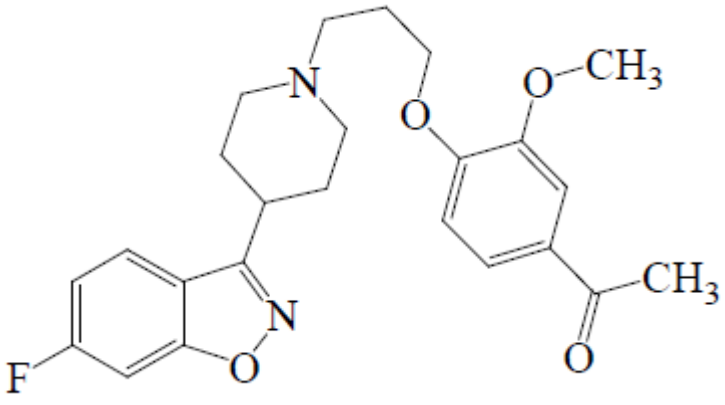

Figure 1 - Structural formula of iloperidone.

The structure of iloperidone was confirmed using a combination of NMR spectroscopy (1D-proton [^{1}H], 1D-carbon [^{13}C], gradient COSY, gradient HSQC, and gradient HMBC), mass spectrometry, FT-IR spectroscopy, UV spectroscopy, thermal gravimetric analysis, DSC, optical rotation and elemental analysis. In addition to the spectroscopic evidence supporting the structure, the three-dimensional crystal structure of iloperidone was determined by single-crystal X-ray diffraction analysis.

The active substance is a white to off-white non-hygroscopic crystalline powder, highly permeable, soluble in organic solvents such as acetonitrile and methanol, moderately soluble in acidic aqueous environments, and sparingly soluble in basic aqueous environments.

Iloperidone has a non-chiral molecular structure.

Only a single crystalline form has been observed for iloperidone. No amorphous form of iloperidone has been observed during the development program. Using DSC and XRPD data it has been demonstrated that there is no change in polymorphic form upon active substance storage.

Manufacture, characterisation and process controls

A single manufacturer carries out the manufacture of the crystalline active substance and a second manufacturer is proposed for milling (micronisation).

Iloperidone is synthesized in six main steps using four commercially available well defined starting materials with acceptable specifications. The synthesis of iloperidone consists of a two branch synthesis in which the two final intermediates are first formed and then condensed in the last step of the chemical synthesis to form crude iloperidone. Three synthesis intermediates are isolated. Crude iloperidone is subsequently crystallised and micronised in order to achieve acceptable blend uniformity.

An optional reprocessing procedure has been defined and validated for the crystallisation step. Batch analysis data for 6 reprocessed batches have been provided demonstrating compliance with the specifications. Reprocessed batches have also been put on stability (long-term and accelerated) with satisfactory results.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. It was initially developed by Hoechst, further optimised by Novartis and finally optimised by the proposed manufacturer. The manufacturing process remained essentially unchanged through the development and through scale-up of the process to the proposed commercial process. Minor process changes occurred throughout development such as solvent changes and processing parameters, however the actual synthetic route and process intermediates have not changed from the initial process. Changes introduced have been presented in sufficient detail and have been justified. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

Process validation was completed using a three consecutive batch prospective validation approach according to an approved protocol. Satisfactory data has been presented demonstrating that the manufacturing process consistently results in an active substance of acceptable quality.

The active substance is packaged in materials which comply with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for: appearance, identity (FT-IR), melting point (Ph.

Eur.), purity (DSC), loss on drying (TGA, Ph. Eur.), related substances (HPLC), residual solvents (GC), heavy metals (ICP-OES), assay (HPLC, potentiometric titration), particle size (laser diffraction), polymorphic form (XRD), sulphated ash (Ph. Eur.), appearance of solution (USP), microbial limits (Ph. Eur.) and bacterial endotoxins (Ph. Eur.).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

Limits for particle size have been appropriately justified.

Several impurities have been identified as potential genotoxic impurities and they are adequately controlled below the TTC.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for identity, assay, in-process testing and impurities testing has been presented.

Batch analysis data (n=1 development scale, n=3 pilot scale used for stability testing and n=6 commercial scale used for process validation) of the active substance are provided. Additional supporting batch results are presented for 24 commercial batches manufactured by the proposed manufacturer for non-EU markets and further validation batches (including reprocessing steps). The results are within the specifications and consistent from batch to batch. Further supporting batch results are provided for 24 early development batches from manufacturers that were used during the development of the product.

Stability

Stability data from 3 pilot and 3 commercial scale batches of active substance from the proposed manufacturer stored in a container closure system representative of the one intended for the market for 48 months under long term conditions at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. Additional supportive data was provided from batches manufactured by different manufacturers used during development only.

The following parameters were tested: appearance, identification by IR, identification by XRD, melting point, loss on drying (in oven), appearance of solution, colour of solution, related substances (Q1-Q7, each unidentified, total unidentified and total related substances), microbial limits and bacterial endotoxins. The analytical methods used were the same as for release and were stability indicating.

All tested parameters were within the specifications.

Photostability testing following the ICH guideline Q1B was performed on a single batch and the results demonstrate that the active substance is not sensitive to light. Therefore a warning to store the active substance protected from light was proposed. Additionally, the forced degradation study results indicate that the active substance is slightly sensitive to light.

Results on stress conditions were provided. Minimal degradation was observed under acidic, basic, high temperature, and high humidity conditions.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 48 months in the proposed container. The proposed storage conditions are “Keep container tightly closed, protect from light”.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is presented as immediate release tablets containing 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg and 12mg of iloperidone. The tablets are white, round, flat, bevelled-edge tablets with the tablet strength debossed on the upper face (e.g., “8” for the 8 mg strength) and a logo debossed on the lower face. The tablet diameters are different for each strength except for the 2 mg and 4 mg strengths, which have the same diameter, but have either a “2” or “4”, debossed on the upper face.

The qualitative and quantitative composition of Fanaptum tablets is presented in **Error! Reference source not found.** below:

The aim of the formulation development was to achieve a physically and chemically stable formulation for clinical development, which could be modified for commercialisation with minimal changes in the formulation and manufacturing process.

As mentioned earlier in the report, iloperidone is a non-hygroscopic crystalline powder that exists in a single polymorphic form. Particle size of the active substance is controlled in order to improve manufacturability.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in paragraph 2.1.1 of this report. The choice of excipients is based on results obtained from active substance-excipient compatibility studies, where the compatibility of binary mixtures of iloperidone and 24 different excipients (1:99) was investigated after storage for 4 weeks. The mixtures were investigated for appearance, assay and degradation products.

The formulation developed by Hoechst (hard capsules and film-coated tablets) was used in Phase 1 and Phase 2 clinical trials. The formulation for the film-coated tablet was essentially the same as that for the capsules except that the powder blend was granulated using water, dried, blended and then compressed into tablets followed by film coating.

Novartis optimised the formulation and subsequently developed an additional capsule formulation. These formulations were used in several Phase 3 clinical studies. The formulations were then further optimized by Novartis, used in additional phase 2 and phase 3 clinical studies and adopted without change by Vanda, and used by Vanda in the final pivotal Phase III clinical trial. The tablet formulation represents the proposed commercial formulation. A bioequivalence study was additionally performed by Vanda showing bioequivalence between the capsule and the proposed tablet commercial formulation.

Fanaptum tablets are manufactured using several unit operations. The manufacturing process has remained relatively unchanged during development.

The discriminatory power of the dissolution method has been considered sufficiently demonstrated.

The proposed primary packaging are either dose titration cards for treatment initiation consisting of blisters placed into a paperboard cards and sealed; or HDPE bottles with a child-resistant closure containing a heat induction seal, for dose maintenance. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of seven main steps.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance, identification (HPLC, UV), hardness (Ph. Eur.), dissolution (HPLC), disintegration (Ph. Eur.), average weight (gravimetric), content uniformity (HPLC, Ph. Eur.), loss on drying (gravimetric, Ph. Eur.), mass uniformity (gravimetric, Ph. Eur.), assay (HPLC), related substances (HPLC) and microbial limits (Ph. Eur.).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for 8 commercial scale batches covering all strengths and confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. Additional data was provided for 43 batches of various scales manufactured by the different manufacturers used during development.

The finished product is released on the market based on the above release specifications, through traditional final product release testing

Stability of the product

Stability data from four commercial scale batches of each of the 1, 8 and 10 mg tablet strengths, five commercial scale batches of each of the 2, 4, 6 mg tablet strengths, and six commercial scale batches of the 12 mg tablet strength stored under long term conditions for up to 60 months at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The batches of medicinal product were identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Additional supportive stability data from 15 batches of the 1, 4, 6, 8, 12 mg tablets manufactured by Novartis, a manufacturer used during development, was provided.

Samples were tested for appearance, hardness, dissolution, disintegration, loss on drying, assay, related substances, friability (in house) and microbial limits (Ph. Eur.). The analytical procedures used are the same as for release, except for tablet friability which was tested at stability only. The analytical procedures used are stability indicating.

All tablets remained within their respective stability acceptance criteria through 60 months of storage at long-term conditions and through 6 months at accelerated storage conditions.

The results for batches provided from both the development and the commercial manufacturers are consistent.

In addition, three batches were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. When stored in HDPE bottles and blisters, Fanaptum tablets were stable as shown by the results for appearance, loss on drying, content of active ingredient and degradation products. Samples of the finished product that were not protected by the container closure system became yellow on the exposed face, showed a decrease in assay and an increase in degradation products. Based on these studies a special precaution for storage - store in the original package in order to protect from moisture and light-, was proposed.

Based on the performed in-use stability study, it is concluded that the finished product is sufficiently stable for 60 days or the duration of use of one bottle taken into account the posology.

Based on available stability data, the proposed shelf-life of 48 months when stored in the original package in order to protect from moisture and light is considered appropriate.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on TSE safety.

2.2.6. Recommendation for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Pharmacology

Iloperidone (also known as HP 873, NVP-ILO522, ILO522, or VYV-683) belongs to the chemical class of piperidinyl-benzisoxazole derivatives and has high (nM) affinity for 5HT2A/D2/D3 receptors in humans and thus acts as an antagonist at selected dopaminergic, serotoninergic, and adrenergic receptors. The primary pharmacodynamic properties of Iloperidone and its main metabolites P88, P89 and P95 were analysed in numerous in vitro, ex vivo and in vivo studies, mostly in comparison to clozapine and haloperidol. These investigations confirmed the antagonistic profile of Iloperidone at dopaminergic,

serotonergic and adrenergic receptors, which is characteristic for the class of atypical antipsychotic agents.

Primary pharmacodynamic studies

In vitro, Iloperidone exhibited high affinity for dopaminergic D2 and D3 receptors and for serotoninergic 5HT2A receptors. It displays a ratio D2/5-HT2A similar to atypical antipsychotics such as risperidone, olanzapine or quetiapine.

It also has affinity for D4 (human), 5-HT1A (rat and human) and sigma (rat) receptors. No affinity was observed for muscarinic receptors, NMDA-ion channel-binding site and glycine-binding sites. It is a competitive antagonist at α1 receptors indicating likely cardiovascular effects. Its affinity for α2 was lower.

Regarding binding to D1 receptors, there is a discrepancy regarding Ki values. The applicant conducted additional experiments to investigate the binding of Iloperidone to D1 and D2 receptors. Results are in line with those obtained in study ILO-1PD-001/Kongsamut with Ki values for D2 short receptor at least 10-fold lower than Ki values for D1 receptor.

Ex vivo, Iloperidone markedly inhibited rat 5-HT2 receptors while the inhibition of D2 receptors was weak.

P89 binds to 5HT2 and D2 receptors with a high affinity. P88 IC50 for D2 and 5–HT2 were 36- and 10-fold lower than P89, respectively. P88 also binds to α1, α2, sigma and H1 receptors.

The in vitro data submitted on the affinity and activity of Iloperidone and its two metabolites P88 and P95 for the 5HT2B receptors have showed mainly an antagonist activity with IC50 value for Iloperidone, P88, and P95 of 1.21×10-7 mol/L, 9.03×10-8 mol/L, and 1.03×10-5 mol/L, respectively. As 5-HT2B agonists are known to be involved in the development of lung and heart fibrosis and heart valve disease it cannot be excluded that antagonists to 5HT2B receptor have no implication in human cardiac toxicity. Since the antagonistic effect of Iloperidone and its two main metabolites P88 and P95 is not investigated, complete knowledge is not available. “5HT2B antagonistic effect” the Applicant has agreed including it as missing information in the Risk Management Plan (RMP), and the effect is not fully investigated.

Iloperidone and P88 bind to sigma receptors. Iloperidone IC50 for sigma receptors was lower than for D2 receptors and P88 IC50 for sigma receptors was in the same range as for D2 receptors. Sigma receptors are known to be involved in addiction, amnesia, pain, depression, neuroprotection and ion channel regulation.

The functional activity of Iloperidone on Sigma-1 and Sigma-2 receptors was not conducted, and thus no data provided to exclude an activity of Iloperidone in these receptors. The necessity to conduct additional studies on dependence potential of Iloperidone remains relevant. However, the Applicant has addressed this issue not by performing additional studies, but by including “Drug Abuse” as Missing Information in the RMP.

P95 has comparable affinity for 5-HT2A receptors, higher affinity for α2 receptors and lower affinity for dopaminergic receptors.

P88 and P95 are major human metabolites. They are pharmacologically active and thus of toxicological relevance.

In rat tissues, Iloperidone was found to be an antagonist to serotonin receptors and to dopamine and α receptors to a lesser extent.

In in vitro functional assay on human receptors, Iloperidone was found to be devoid of agonistic activity at D2A, D3, α2A, α2C and 5-HT6. It was found to act as an antagonist at human dopaminergic, noradrenergic and serotoninergic receptors.

Both enantiomers of P88 exhibited antagonist activity to α2C and D2A receptors with similar affinity to Iloperidone suggesting a potential to exert similar pharmacological activity on dopaminergic and adrenergic receptors.

Iloperidone exhibited high affinity for human dopamine D2 and D3 and for human serotonin 5-HT2A receptors, and also exhibited affinity for dopamine D4, and for serotonin 5-HT2C, 5-HT6, and 5-HT7 receptors. Iloperidone displayed relatively lower affinity for dopamine D1 and D5 receptors.

Iloperidone exhibited a high affinity for α1-noradrenergic and 5-HT2-serotonergic receptors, a moderate affinity for α2-noradrenergic, D2-dopaminergic, 5-HT1A-serotonergic, and sigma receptors, and low affinity for D1-dopaminergic and 5-HT3-serotonergic receptors. Iloperidone had no apparent affinity for muscarinic receptors, the [3H]TCP-binding site of the NMDA-receptor channel, or the glycine-binding site associated with the NMDA-receptor channel.

Iloperidone was shown to be a potent antagonist of norepinephrine (NE)-induced contraction of isolated rat aortic rings as well as a competitive antagonist at vascular α1A-receptors in the rat mesenteric arterial bed. These pharmacodynamics effects are considered significant for cardiovascular effects in vivo.

Pretreatment with Iloperidone (10 mg/kg i.p.) to rats markedly inhibited 5-HT2 receptor-binding ex vivo, and weak effects on D2 receptors was similar to what was seen with clozapine at doses of 10 to 40 mg/kg i.p. The high 5-HT2/D2 receptor binding ratio of Iloperidone is consistent with other atypical antipsychotic agents and suggests that Iloperidone may display antipsychotic activity with a reduced risk of extrapyramidal symptom (EPS) liability.

The receptor binding characteristics of the three major Iloperidone metabolites P88, P89 and P95 were analysed separately in preparations from mice, rats, guinea pigs, monkeys and humans. Metabolite P89 bound with high affinity to 5 HT2 and D2 receptors, whereas P88 showed weaker activity at each of these sites. Both P88 and P89 also exhibited affinity for 5-HT1A receptors, α1 noradrenergic receptors, α2-noradrenergic receptors, and sigma opiate receptors. P95 exhibited similar affinity for the human 5-HT2A receptor compared with Iloperidone, and exhibited higher or comparable affinity for each adrenergic receptor subtype tested as compared with Iloperidone.

In vivo, single doses of Iloperidone significantly increased dopa accumulation in both the striatum (0.30 to 10 mg/kg) and the nucleus accumbens (1 to 10 mg/kg) in rats after intraperitoneal administration. Only slight enhancement was seen in cortical slices of rat brain, when Iloperidone was tested for its ability to modify electrically stimulated release of [3H]NE. This result could indicate α2-antagonist properties of Iloperidone. In whole rat brain synaptosomal preparations, Iloperidone was a moderately potent inhibitor of serotonin uptake.

In cell lines expressing human receptors, Iloperidone was found to be devoid of any agonist activity against dopaminergic, serotonergic, or noradrenergic receptor subtypes. On the other hand, it significantly and concentration-dependently antagonized the D2 and D3 response to dopamine and also significantly antagonized the agonist response of the adrenergic α2C and α2A receptor subtypes.

The metabolite P88 and its enantiomer R(+)-P88 inhibited the cAMP reduction induced by agonists against α2C-adrenergic and D2-dopaminergic receptors with similar affinity than the parent compound.

Inhibition of L DOPA accumulation by apomorphine was reversed by Iloperidone and its metabolites P88 and P89 after i.p. administration to rats, consistent with an atypical antipsychotic profile.

Chronic treatment of rats with Iloperidone at 5 mg/kg/day i.p. did not significantly change the number or affinity of D2 receptors in any region of the corpus striatum or the nucleus accumbens while the same treatment significantly down-regulated cortical 5-HT2 receptors in the frontal cortex comparably to what was seen for clozapine.

Results from s.c. administration of Iloperidone to rats suggested no 5-HT1A antagonist activity in vivo in this species. This finding contrasts in vitro findings, and may reflect a difference in affinity for the rat and human 5-HT1A receptor subtype.

The ability of Iloperidone to antagonize the pressor effect of i.v. administered phenylephrine and serotonin was evaluated in pithed rats. Oral administration of 1 and 6 mg/kg Iloperidone produced a non-competitive blockade of the serotonin-induced pressor response.

The effects of Iloperidone when evaluated in behavioural assays conducted in mice, rats, and monkeys and support the dopaminergic, serotonergic and noradrenergic blockade previously shown in receptor affinity and functional characterisation studies. This supports an antipsychotic potential of Iloperidone. Iloperidone was also associated with anxiolytic properties and increased social interaction in various models for anxiolytic/negative symptom and social withdrawal efficacy. No sedative activity was found in the rat pole-climb avoidance test. In general the ED50-values for Iloperidone in the various behavioural studies were lower than for clozapine but higher than haloperidol, although based on comparisons based on mg/kg doses, which makes interpretations somewhat difficult. Together with receptor affinity data and functional characteristic data these studies support the Applicant's proposed mode of action for Iloperidone.

Iloperidone treatment (1 mg/kg i.p. for 21 days) produced an increase of expression levels of D2 receptors in the hippocampus and striatum of rats, indicating relevant D2 receptor blockade. Expression of GABA-related genes reelin, GAD67 and GAT-1 was markedly increased and the results indicate a potential of Iloperidone to either directly or indirectly affect expression levels of a number of gene products which may play a role in the aetiology of schizophrenia.

Secondary pharmacodynamic studies

Iloperidone exhibited potential analgesic activity in mice after s.c. dosing (ED50 = 0.03 mg/kg).

Although less potently than haloperidol, Iloperidone blocked apomorphine-induced stereotypy and induced catalepsy in rats, and at doses of 1.5 and 3 mg/kg, Iloperidone significantly decreased haloperidol-induced catalepsy in rats 60 and 120 minutes after dosing. These effects may indicate a potential to ameliorate some of the EPS seen with dopamine-receptor blockade.

Safety pharmacology programme

Data indicate that Iloperidone and its metabolite P88 at free plasma concentrations of 0.1 µM and above are likely to have direct effects on the QRS complex, QT duration, and cardiac conduction, and also more pronounced compared to other antipsychotic drugs.

Iloperidone showed higher affinity for hERG channel than other antipsychotics and prolongation of action potential in Purkinje fibers. When compared to human exposure at 12 mg BID, the IC50 for hERG inhibition are below the total Cmax in humans at 12 mg BID (Cmax = 32.14 ng/mL = 75 nM) and only 5.5 to 7-fold higher than the unbound Cmax (fu = 7%). Therefore, hERG channel inhibition has the potential to be clinically relevant.

P88 and P95 produced the same effects as Iloperidone on hERG channels and Purkinje fibers. P88 showed these effects at concentrations close to those seen with Iloperidone while P95 was less active. When compared to human exposure at 12 mg BID, P88 IC50 for hERG inhibition is in the range of the total Cmax in humans at 12 mg BID (Cmax = 37.09 ng/mL = 87 nM). P95 IC50 is at least 30-fold higher than human total Cmax and at least 200-fold higher than human unbound Cmax (In humans, Cmax = 37.74 ng/mL = 138 nM, fu = 15%). Therefore, P88 hERG channel inhibition has the potential to be clinically relevant.

As shown in Table 1, the Iloperidone free therapeutic plasma concentration may be as low as 8.4-fold at the lowest reported plasma protein binding.

Table 1 - hERG IC50/Cmax values for Iloperidone, P88 and Ziprasidone.

	Iloperidone	P88	Ziprasidone
MW	427	431	412
hERG IC50 nM	29	56	55
hERG IC50 ng/mL	12.4	24.1	22.6
Cmax total ng/mL	21	24	168
Protein binding %	93-99%*	98%**	99.9%
Cmax u ng/mL	0.21-1.47	0.48	0.168
hERG IC50/Cmax	8.4-59.0	50.2	134.5

* studies TH1D150793, DMPK(US)N01-1200, XS-0531; ** study XS-0531 ; the 85% value used in previous calculations was probably that reported for metabolite P95 in study DMPK(US)R99-1121

In agreement with the hERG study findings, Iloperidone and P88 concentration-dependently prolonged action potential duration in dog ventricular Purkinje fibres at concentrations of 0.1 µM and above. At a high concentration of 10 µM of Iloperidone and its P88 metabolite, some reduction of the maximum rate of depolarization was observed.

Despite the hERG findings, no changes in ECG parameters were recorded in the performed studies with Iloperidone in dogs, where exposure seems to be lower than humans.

Redfern et al (2003) performed a retrospective analysis of literature hERG data indicated that block of hERG currents is associated with TdP arrhythmias if it occurs at concentrations close to those achieved in clinical use, and a 30-fold margin between free therapeutic plasma concentrations and IC50 values for block of hERG currents are stated to be a line of demarcation between the majority of drugs associated with Torsade des Points arrhythmias and those which are not.

The non-clinical effects of Iloperidone and its P88 metabolite indicate a high torsadogenic potential at clinically relevant doses.

2.3.2. Pharmacokinetics

Pharmacokinetics studies were conducted in vitro and in vivo with mice (CD-1), rats (Sprague-Dawley, Han Wistar, Lister Hooded, Long Evans, Wistar-Hannover, Long Evans Hooded), rabbits (New Zealand white), dogs (Beagle), and monkeys (Cynomolgus), and evaluated oral or intravenous (i.v.) administration of Iloperidone following single and multiple doses for up to 14 days.

After single i.v. administration of Iloperidone, Cmax was always reached in all species at the first blood sampling time (5 min). In contrast, Tmax differed following either single or repeated oral administration from 0.5 and 1 h in CD 1 mice and Beagle dogs, 1 and 2 h in SD rats as well as 1 h in NZW rabbits and Cynomolgus monkeys. Oral bioavailability was low across species, most probably owing to first-pass metabolism. After p.o. administration of 5 mg/kg Iloperidone, 5 % of the dose was detected in mice, < 1 % in rats and 19 % in rabbits and dogs. The low bioavailability is attributed to a first-pass effect.

Based on Cmax and AUC, dogs were generally exposed to higher levels than other species independent of the i.v. or p.o. route. Moreover, single and multiple dosing of rats resulted in higher mean AUC values in females than in males suggesting a possible gender difference with is in agreement with a tendency observed in dogs and clinical effects. After a 14-day dosing in mice, exposure was similar in males and females while in rats and dogs, females seemed to be more exposed than males after 5 days and 14 days respectively.

Iloperidone exhibited high in vitro protein-binding in rats, dogs and humans of 90, 86 and 93 %, respectively. Following i.v. or p.o. administration, Iloperidone showed rapid distribution with highest levels in liver, kidney, gastrointestinal system and secretory glandular tissues, while CNS availability and placental transfer were limited. On the contrary, Cmax in plasma and milk of lactating rats was determined at 0.5 and 4 h after p.o. administration of 5 mg/kg culminating in 10 fold higher concentrations in milk compared to plasma.

Iloperidone is rapidly and extensively distributed into tissues with highest concentrations measured in gastrointestinal system, kidney, liver, adrenals and secretory glandular tissues. In pigmented rats, high concentrations were found in the eye and the skin, indicating melanin-binding.

After repeated doses, P95 exposure was measured in mice, rats and dogs. P95 is a major metabolite in humans where exposure to p95 is higher than exposure to Iloperidone. P95 bioavailability was 18-32% in mice and 1.4 -2.6% in rats. P88 was also measured in rats while most of the dogs had no measurable P88 concentrations even at the highest dose. P88 is also a major metabolite in humans achieving higher exposure than Iloperidone. Only the S-form of P88 is formed in humans. P88 bioavailability was 2% in mice and 5% in dogs indicating extensive first-pass. In mice the overall metabolite patterns in the plasma and excreta were qualitatively similar to those in mice dosed orally with Iloperidone, suggesting a possible rapid conversion of S-P88 to Iloperidone in the mouse. P88 is formed from Iloperidone by reduction of exposure of the carbonyl of the acyl side chain. In addition to the parent compound, the metabolite P88 also showed potential to cross the blood-brain-barrier, whereas P95 was undetectable in brain tissue. Furthermore, Iloperidone was shown to enrich in skin and uveal tract pointing towards melanin-binding activity.

Iloperidone was found to be extensively metabolised with P88, P89, P94 and P95 constituting the main metabolites. In vitro biotransformation was observed by N-dealkylation (P22), hydroxylation (P94), O demethylation (P89) and carbonyl reduction (P88). Unchanged Iloperidone and its metabolites were predominantly eliminated by faeces across species.

The potential of Iloperidone and its metabolites P95 and P88 to inhibit human cytochrome P450 (CYP) enzymes was assessed. The data indicate that Iloperidone and its metabolites does not have enzyme inducing properties, specifically for the cytochrome P450 isozymes: CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP3A4 and CYP3A5. It is however possible, though, that Iloperidone may be a CYP3A4/5 inhibitor and a CYP3A4 mRNA inducer. The potential of Iloperidone to induce liver-metabolizing enzymes was evaluated in rats. Hepatic biochemical evaluations revealed that treatment with Iloperidone for 2 weeks had no effect on total P450 activity, glutathione content, glutathione S-transferase activity, or microsomal and total liver protein levels.

Iloperidone and its metabolites, P88 and P95, were evaluated as substrates and/or inhibitors of the human efflux transporter MDR1 in Caco-2 cells. The results suggest that the permeability of P95 across Caco-2 cells may be influenced by MDR1, all though the effect is not significant. Furthermore, Iloperidone, P88 and P95 were not considered substrates of the transporters BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, and MATE2-K.

2.3.3. Toxicology

The non-clinical toxicity of Iloperidone, a potential antipsychotic agent, and the main Iloperidone metabolite in humans, P95 are discussed, including acute and chronic toxicity, genotoxicity, reproductive toxicity, and carcinogenicity.

Single dose toxicity

Acute-dose toxicity studies with Iloperidone were conducted in rats and mice following oral, intravenous and intraperitoneal routes of administration. Approximate median lethal oral doses following single administration to mice were found to be in the range of 55 and 80 mg/kg (males) and <55 (females) mg/kg. In rats the median lethal doses were significantly higher with >480 mg/kg in males and between 240 and 480 mg/kg in and females, respectively.

Repeat dose toxicity

Repeat-dose toxicology studies with Iloperidone were conducted in mice, rats, rabbits and dogs up to 3 months, 26 weeks in rats and 12 months in dogs following oral, intravenous or inhalative routes of exposure. The MTDs of Iloperidone determined in these studies were 5 mg/kg p.o. in mice, 12 to 25 mg/kg p.o. in rats, 5 mg/m3 inhaled for rats, 3 mg/kg i.v. in rabbits, and 6 to 25 mg/kg in dogs. A NOEL of 10 mg/kg was determined in dogs treated for 13 weeks (only based on pathology findings not clinical observations). The longest study duration of the oral toxicity studies were in rats and dogs with 26 weeks and 12 months, respectively. The no observed adverse effect levels (NOAEL) were determined to 12 mg/kg by the 6-month rat study and 6 mg/kg by the 12-month dog study (equivalent to 72 mg/m2/day in rats and 120 mg/m2/day in dogs). Based on dose level calculated by body surface areas, the NOAELs in rats and dogs are approximately 4.9 and 8 times greater than the maximum recommended clinical dose (24 mg/day) for Iloperidone, respectively. The ratios between animal/human systemic exposure become even lower than initially proposed when calculating using NOAEL values. Thus, for rats (12 mg/kg/day), the ratio is 0.89/3.6 (for males and female animals, respectively) and for dogs (6 mg/kg/day) it is < 1. The Applicant states that '*low exposure/safety margins between human and preclinical species can nevertheless be appropriately monitored and managed in human clinical care situations*'. Such low safety margins are not usually acceptable for indications that do not include life-threatening diseases and could be considered in the benefit/risk profile of the product.

CNS-related clinical signs were consistently observed in all tested species at all dose levels. They mainly consisted in decreased spontaneous activity, ptosis of the eyelids, prostration, relaxed scrotum (in rats) and bizarre behaviour (in dogs). Due to the CNS related pharmacodynamics clinical signs observed it can be discussed whether NOEL were established. Therefore, it is also questionable whether NOAEL can be established for the pivotal studies. Iloperidone administration did also induce a decrease in leukocytes in the three species and was generally accompanied by a decrease in lymphocytes. Bone marrow decreased cellularity was observed in mice and rats. Decreased platelet count and coagulation times was seen in rats. Lymphoid necrosis was observed in mice and attributed to stress. Bone marrow decreased cellularity was found in mice and rats. Increased cholinesterase levels was detected in male rats in a 4-week study but was not reproduced in the 13-week study.

In mice oral administration of Iloperidone at 5, 10 and 20 mg/kg for 13-weeks caused early deaths and lymphoid necrosis of multiple lymphoid organs. Histological findings in lymphoid organs were interpreted to be induced secondary by elevated systemic levels of glucocorticoids released by the adrenal cortex in response to stress. Due to the severe toxicity/high death rate observed in this study, the clinical relevance

of these findings seems to be low. No similar findings in lymphoid organs were reported from other test species or clinical studies in humans.

In rats repeated oral dosing (up to 26 weeks) revealed treatment related findings related to the CNS (decreased spontaneous activity, ptosis and relaxed scrotums) and prolactin stimulation due to exaggerated pharmacodynamic activity of Iloperidone, i.e antagonistic activity at D2-, 5 HT2A- and α1-adrenergic receptors. Elevations in prolactin levels are considered responsible for the effects seen in mammary gland (vacuolization, hyperplasia), female genital tract (uterus weight), with additional effects on the male accessory sex organs (testes and prostate) at higher exposures. Whereas effects on muscle such as ptosis and relaxed scrotums and vaginal openings could be related to engagement of adrenergic receptors. This finding is appropriately reflected in the proposed SmPC. In clinical studies, Iloperidone showed less pronounced serum prolactin increases in patient when compared with other atypical antipsychotic agents.

In dogs treatment related clinical signs were primarily related to the CNS and included decreased spontaneous activity and/or crouching posture, tremors, bizarre behaviours, laboured breathing, scleral infection, ptosis of the eyelids, prolapsed nictitating membranes, and glassy eyes at all dose levels. The measured concentrations were low and no dose dependency was observed. The highest achievable exposure was comparable to human exposure which suggest no safety margins. The clinical signs were not observed during the recovery period. Slightly higher liver weights and enlarged hepatocytes consistent with hepatocellular hypertrophy due to proliferation of the endoplasmic reticulum (males ≥ 24-mg/kg). However, no dose limiting toxicities were observed and no NOAEL could be identified in the pivotal studies.

Genotoxicity

Iloperidone is not genotoxic based on in vitro and in vivo assays (ames test, mouse bone marrow micronucleus test, rat hepatocyte micronucleus test, chromosomal aberration) except under strongly cytotoxic conditions. However, micronized Iloperidone was found to induce chromosomal aberrations in CHO cells under both metabolic activation and non-activation conditions, the effect was seen over a narrow, cytotoxic dose range. The dose-effect curve was considered to be typical for high-toxicity clastogens and therefore of little biological significance and the results obtained from in vitro chromosomal aberrations assays are not considered relevant and Iloperidone can be considered to be a non-genotoxic.

Carcinogenicity

A two-year carcinogenicity study in mice using dose levels of 2.5, 5, and 10 mg/kg revealed increased incidence of malignant mammary tumors in females at the lowest dose. In addition, the incidence of mammary duct ectasia/galactoceles and glandular hyperplasia was increased in all treated females. Prolactin levels were elevated in male and female mice in the study, however, no dose relationship were observed in females. This reflected in section 5.3 of the proposed SmPC. The clinical relevance of these findings is unknown.

Toxicokinetic evaluation showed exposure levels (AUC) in the high dose slightly (1.4 fold) above the human exposure at 12 mg BID. Hence, no safety margin can be established. Furthermore, treatment-related lesions were noted in the heart (cardiomyopathy and/or atrial thrombosis) and lungs (chronic interstitial inflammation/fibrosis and alveolar macrophages). According to the Applicant cardiomyopathy is a common, spontaneous lesion in aging laboratory mice, but an increased incidence

and severity in treated males and females suggested that the test article may have exacerbated the spontaneous lesion.

Reproduction Toxicity

The potential reproductive and developmental toxicity of orally administered Iloperidone was evaluated in four studies. Iloperidone had no effect on male fertility, was non-teratogenic, and at doses that did not cause significant maternal toxicity had limited effects on fetal and neonatal development. However, Iloperidone is considered to affect female fertility. This is likely the consequence of a treatment-related increase in prolactin levels which induced estrous cycle disturbances (prolonged diestrus) and a decrease in the number of corpora lutea. No studies in juvenile animals have been performed.

Potential adverse effects of iloperidone for embryo-fetal development were investigated in conventional studies performed in rats and rabbits. In rats, a high level of early post-implantation loss was reported at ≥16 mg/kg/day. At 64 mg/kg/day, fetal weight and length were reduced, and the incidence of skeletal variations and minor anomalies was increased. Due to the high post-implantation loss, the number of foetuses examined for malformations was much lower at the high dose level. Considering also the minor skeletal anomalies reported at this maternotoxic dose level, a firm conclusion on the lack of teratogenic effect cannot be drawn. At 16 mg/kg/day, the increased incidence of skeletal variations and decreased fetal weight in spite of unchanged fetal weight suggest some treatment-related embryo-fetal toxicity. In the “extended” fertility study, the incidence of visceral variations was increased at 36 mg/kg/day (high dose level). Overall, the NOAEL for rat embryo-fetal development is 4 mg/kg/day. In rabbits, embryo-fetal toxicity was reported at the high (maternotoxic) dose level only. It consisted mainly in an increase in post-implantation losses. In this group, the incidence of foetuses with a large or displaced stomach (25%) was increased vs. study control (5.1%) or historical controls (12.1%). Overall, the NOAEL for rabbit fetal development is 10 mg/kg/day.

In the peri- and post-natal toxicity study, the noteworthy findings observed at the mid and high dose levels were prolonged gestation and parturition, increased neonatal and postnatal mortality due notably to poor maternal care as a result of excessive pharmacodynamics effects (e.g. sedation). In the post-weaning period, offsprings of dams treated at 36 mg/kg/day were smaller than those of other groups. Otherwise, post-weaning growth and development of the F1 animals was not adversely affected by treatment. Similar effects were observed in the extended fertility study in animals (and their offsprings) treated at dose levels lying in the same range from 2 weeks pre-mating to weaning. In both studies, the NOAEL for both dams and their progeny was 4 mg/kg/day.

Toxicokinetic evaluations were not performed in any of these studies which makes more difficult to perform any risk assessment. In rats, it could be relied on the exposure data obtained in the only toxicity study where AUC values were calculated, i.e. the 4-week toxicity study (no.0394-220), although animals were non-pregnant. At the NOAEL determined for female fertility, pre- and post-natal development, animals were less exposed than patients at the maximum recommended dose (12 mg twice daily).

Other toxicity studies

Additional non-clinical studies did not reveal any toxic effects of iloperidone on the immune system in rats, neither was iloperidone found to be ototoxic in guinea pigs, or a dermal or eye irritant in rabbits.

Iloperidone and P88 seem to have a high affinity for sigma receptors that are involved in addiction. A clinical evaluation of dependence was not conducted.

Iloperidone is positive in the 3T3-NRU test and is distributed into melanin-containing tissues particularly in the eye. Eye disorders were reported in clinical trials.

Phototoxic potential of Iloperidone has not been investigated. Considering that the phototoxic potential of iloperidone cannot be ruled out, and in absence of dedicated non-clinical and/or clinical studies to assess this potential, the Applicant agreed to include it as an important potential risk in the RMP.

Studies with P88

P88 is a major metabolite in humans where its exposure is higher than iloperidone exposure whereas P88 levels were very low, if any, in rats and dogs. The Applicant conducted only single-dose studies in the rat and the rabbit and two genotoxicity tests (Ames and chromosomal aberrations).

P88 interconverts with Iloperidone. In rats, the equilibrium of the reduction/oxidation reaction favoured Iloperidone. Iloperidone:P88 AUC ratios reached 19.1 in rats treated with Iloperidone at 16 mg/kg for 5 days, and 0.69 in humans given 12 mg Iloperidone. In these studies, P88 levels in humans were 6.8-18.6-fold higher than those in rats. Taking into account the dose levels used in toxicity studies performed with Iloperidone (48 mg/kg/day in 26-week study), conducting additional studies with Iloperidone in rats to reach human P88 levels is not viewed as feasible. Since exposure to Iloperidone is also higher than exposure to P88 in rats treated with P88 (6-9-fold at target exposure levels), performing additional toxicity studies with P88 is not considered as relevant. In rabbits, the formation of P88 from Iloperidone is one of the major biotransformation pathways of Iloperidone (iloperidone:P88 AUC ratio of 1.8 after a 5 mg/kg oral dose, study DMPK(US) R99-1190).

Considering the interconversion of Iloperidone and P88, and their similar receptor binding profile, it seems acceptable to use the sum of Iloperidone and P88 to perform exposure assessments. Additional studies are not deemed necessary to qualify P88 since it could be relied on rat/rabbit studies performed with Iloperidone to cover general toxicity, in vivo genotoxicity, and reproduction toxicity.

Single dose toxicity

In single dose studies in rats and rabbits, P88 induced CNS clinical signs similar to those observed with Iloperidone. In rats, it also induced decreased testes weight. The NOAEL was set at 10 mg/kg in males corresponding to a safety margin of 0.7 in terms of Cmax and 0.05 in terms of AUC and 50 mg/kg in females corresponding to 8.4 in terms of Cmax and 2.7 in terms of AUC (P88 Cmax =37.09 ng/mL and AUC0-12 = 335.5 ng.h/mL in humans after administration of 12 mg BID). In rabbits, a decrease in food and water consumption at the highest dose was observed. The NOAEL was set at 10 mg/kg in males corresponding to a safety margin of 2.8 and 6.0 in terms of Cmax in males and females respectively and 1.3 and 2.0 in terms of AUC in males and females respectively. After administration of P88, exposure to Iloperidone is higher than exposure to P88 demonstrating a significant conversion of P88 to Iloperidone.

Genotoxicity

P88 was negative in an Ames but produced doubtful results in a chromosome aberrations test in CHO cells.

Studies with P95

P95 is the primary metabolite of Iloperidone in humans with approximately 6 – 10 fold higher exposure when compared to rats and mice. In contrast to the rodent species, the proportion of the P95 metabolite in dogs and rabbits is better comparable to those in humans. Due to this proportional difference in exposure to P95 following Iloperidone administration in preclinical species compared with that in human,

twelve toxicology studies in rats and mice were conducted with the pure P95 metabolite. The extensive toxicological programme conducted with P95 included an acute toxicity study in mice, two 13-week and a 26-week oral repeat-dose toxicity studies in rats, a full battery of in vitro and in vivo genetic toxicity tests, an embryo-fetal development- and a two year carcinogenicity study in rats. Furthermore, immunotoxicity was evaluated in conjunction with Iloperidone in rats and the phototoxic potential of the P95 and P88 metabolites was assessed in a neutral red uptake tests using balb/c 3T3 fibroblast cells.

The clinical signs and observations seen in Iloperidone and P95 rodent multiple-dose studies were similar, although there were some differences. The predominant clinical signs associated with P95, as with Iloperidone, were ptosis, decreased spontaneous motor activity, relaxed and/or reddened scrotum, and relaxed vaginal opening. Test article-related effects were noted in mammary gland (hyperplasia with secretion), female reproductive tract (uterine, vaginal and/or ovarian changes), and adrenal (cortical hyperplasia) in rat Iloperidone and P95 studies. These changes were considered to be due to a exposure-based pharmacologically mediated effect of each compound on the adrenergic and/or dopamine receptors.

In order to further evaluate the observed proliferation in various tissues, a 2-year carcinogenicity study in rats was performed. The results in the 2 year rat carcinogenicity study were comparable with the expected range of toxicity and neoplastic findings expected from chronic studies and with increased prolactin release. No increase in malignant carcinomas was observed. The liver and renal toxicity were observed at doses exceeding the MTD and were associated with early deaths and decreased survival rate. Neoplastic findings related to treatment with P95 were seen in the pancreas, kidneys, and pituitary. Males given 200 mg/kg/day showed an increased incidence of pancreatic islet cell adenoma, and females given 400/250 mg/kg/day showed a small increase in the incidence of tubular adenoma in the kidneys (not considered relevant to humans as this dose exceeded the MTD and associated with renal tubular degeneration/necrosis). At all dosages in males there was an increased incidence of adenoma of the pars distalis though there was no dose-response. The neoplastic changes in the pancreas and pituitary glands of males were considered consequences of prolonged hyperprolactinaemia, and would correlate with the hyperplastic changes seen in pituitary and pancreas seen in the 26-week study. Although no increase in malignant carcinoma was observed an increase in adenoma was observed in males in all treated groups in pancreatic B- islet cell and pituitary pars distalis. Increases in adenoma observed in females occurred only at dose levels with multiple higher exposure than human exposure. The Applicant acknowledges that the incidence of adenomas of the pars distalis in rats was significantly increased in all treated male groups and indeed exceeded the historical range reported from participating laboratories. These findings seem to be in line with the mode of action for the P95 metabolite, acting as a dopamine antagonist. As release of prolactin from the anterior pituitary is inhibited by dopamine, antagonism of dopamine by P95 would be expected to reduce the effect of dopamine and thereby stimulate prolactin secretion. This continuous stimulation of the anterior pituitary with increased and persistent production of prolactin is considered the likely cause of the increased incidence of pituitary adenoma in males. By contrast, the lack of detectable response in females was attributed to the high background level of this finding in female Han Wistar rats. The views of the Applicant seem plausible and are agreed.

As with pituitary adenoma, the increased incidence of pancreatic islet cell adenoma in high dose male rats could be attributed to the pharmacological action of P95. Persistently increased stimulation of DNA synthesis via prolactin receptors in pancreatic islets (Nielsen et al. 1999) through non-genotoxic mechanisms could result in the small increase of islet cell tumours via non-genotoxic mechanisms. The Applicant states that '*importantly, the increased incidence of pancreatic islet cell tumours at 200 mg/kg/day occurred at supra-pharmacologic exposure levels that are not clinically relevant*'. This view is not agreed as safety margins should be derived from the exposure levels at NOAEL. This would yield human:rat exposure ratios of 17.4 (female rats at 150 mg/kg/day) which is not considered large for a product which is intended for lifetime administration. Wording regarding pituitary and pancreatic islet cell

adenoma findings in rats are included in section 5.3 of the proposed SmPC. The clinical relevance of these findings is still not entirely clear. Non-neoplastic findings considered related to treatment with P95 were seen in the kidneys, adrenals, mammary tissue and reproductive organs. There was an increased incidence of chronic progressive nephropathy at all dose levels in females, and a slightly increased incidence and severity of chronic progressive nephropathy and an increased incidence of interstitial inflammation in males given 200 mg/kg. According to the Applicant, and with reference to one publication (Hard et al., 2009), chronic progressive nephropathy (CPN) is a renal disease of unknown aetiology that occurs with high incidence in laboratory rats and has no human counterpart. CPN can be enhanced by chemical exposure (as seen in the P95 carcinogenicity study), but this enhancement is not viewed as a hazard indicator for humans due to major biologic and pathologic differences in renal disease between the two species. These differences are acknowledged.

The Applicant proposes that renal tubular tumour formation is attributable to the inherently proliferative nature of CPN-affected tubules rather than to any tumorigenic potential of P95. Furthermore, in the 2-year P95 bioassay, renal tubular adenomas were seen at low incidence in rats given doses that not only exceeded the MTD but also produced significant kidney and liver toxicity. Hepatic metabolic capacity was likely overwhelmed, leading to increased renal excretion and subsequent nephropathy.

Finally, the P95 exposures of the adenoma-bearing females were at 62-fold (week 13) and 42-fold (week 26) the estimated human clinical exposure to metabolite P95. As renal effects can be clinically monitored, the low incidence of renal tubular adenoma in the rat lifetime study was not considered to be relevant to humans in a clinical situation. This view is endorsed in relation to risk of tubular adenoma formation.

No P95 genotoxicity was observed in a rat micronucleus assay, the Ames test, or a chromosomal aberration assay conducted in cultured CHO cells. No maternal or developmental effects were observed when administered during organogenesis to pregnant rats at exposure levels 22 x the human exposure. In addition, in vitro phototoxicity studies in Balb/c 3T3 fibroblast cells indicate that iloperidone metabolites P95 and P88 are not phototoxic. There was no incidence for an immunotoxic P95 potential in a 4 week study in rats.

A large number of studies on “Iloperidone intermediates” or “production intermediates” were included in the dossier. Several Iloperidone production intermediates were not considered to be mutagenic in either the presence or absence of metabolic activation. Although one of the intermediates was not found to be mutagenic in the absence of metabolic activation, this test article was found to be mutagenic in the presence of metabolic activation. Another Iloperidone intermediate, which has a structure thought to be associated with mutagenicity, was found to induce chromosomal aberrations in cultured CHO cells. Two additional potentially genotoxic impurities have been identified.

The proposed limits for a Iloperidone related impurity (0.8%) is above the ICH Q3A qualification threshold (given a maximum clinical dose of 24 mg/day), but has subsequently been qualified in nonclinical studies. According to the lots of API that were used in the nonclinical safety studies; this impurity was only present at a level of 0.44%.

A computational chemistry-based assessment of this impurity was submitted. The Applicant has used ToxTree and VEGA software as a knowledge-based rule system and a suite of QSAR/statistical toxicology modelling program, respectively. According to ICH M7, *‘The absence of structural alerts from two complementary (Q)SAR methodologies (expert rule-based and statistical) is sufficient to conclude that the impurity is of no mutagenic concern, and no further testing is recommended.*

An expert statement as well as the original reports from the two (Q)SAR analyses were submitted. In the summary of the report it is stated that ‘*Several compounds were assessed with a single low-confidence or moderate-confidence positive QSAR prediction for non-genotoxic carcinogenicity, but the isolated nature of the findings and the absence of predictive confidence, we determine that it is unlikely that the*

compounds present a toxic threat at the very low concentrations manifest in the Iloperidone drug substance.'

2.3.4. Ecotoxicity / environmental risk assessment

The applicant argues that Iloperidone is unlikely to represent a risk to the environment with respect to surface water, ground water and micro-organism. Also, as Iloperidone has a log10Kow value which is not >3 at pH7, the fish bioaccumulation study is not triggered. Some questions still remain regarding the results on the adsorption-desorption and transformation in water sediment systems as Iloperidone is considered not to be readily biodegradable. Reports for algae (OECD 201), Daphnia (OECD 211), and fish (OECD 210) are included in this submission. The transformation study report (OECD 308) and an updated ERA report also have been included in this submission. The Applicant agreed to provide the study report for sediment dwelling organisms when available (planned for January 2018).

2.3.5. Discussion on non-clinical aspects

The non-clinical dossier for Iloperidone is considered sufficient for assessment of pharmacodynamics, pharmacokinetics and toxicology of both the parent compound and the major metabolites, P88 and P95.

Iloperidone receptor binding profile is similar to other members of the class of atypical antipsychotic drugs. Regarding binding to D1 receptors, there was a discrepancy regarding Ki values. The applicant conducted additional experiments to investigate the binding of Iloperidone to D1 and D2 receptors. Results are in line with those obtained in study ILO-1PD-001/Kongsamut with Ki values for D2 short receptor at least 10-fold lower than Ki values for D1 receptor.

Most characteristically for this class of agents is the higher affinity to 5HT2A compared to D2 receptors suggesting a reduced propensity for EPS development in comparison to typical antipsychotics like Haloperidol. The in vitro data submitted during the procedure on the affinity and activity of Iloperidone and its two metabolites P88 and P95 for the 5-HT2B receptors have showed mainly an antagonist activity with IC50 value for Iloperidone, P88, and P95 of 1.21×10-7 mol/L, 9.03×10-8 mol/L, and 1.03×10-5 mol/L, respectively. As 5-HT2B agonists are known to be involved in the development of lung and heart fibrosis and heart valve disease it cannot be excluded that antagonists to 5HT2B receptor have no implication in human cardiac toxicity. Since the antagonistic effect of Iloperidone and its two main metabolites P88 and P95 is not investigated, complete knowledge is not available. For “5HT2B antagonistic effect” the Applicant has agreed including it as missing information in the Risk Management Plan (RMP), since the effect is not fully investigated.

Incidence of atrial thrombosis was also increased in treated mice and was an underlying cause of treatment-related mortality. Cardiac lesions were considered as causative of lung lesions. These findings are reported in the proposed SPC 5.3.

The pharmacological effects of Iloperidone were confirmed in a variety of animal models of serotonin- and dopamine- mediated behaviours and may support potential effective treatment of schizophrenia, including potential anxiolytic activity in the absence of sedative effects.

The applicant relies on FANAPT experience where it is not a controlled substance (US PI section 9.1 and 9.2 (5/2016)), where FANAPT has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. While the clinical trials did not reveal any tendency for drug-seeking behaviour, these observations were not systematic and it is not possible to predict on the basis of this experience the extent to which a CNS active drug, FANAPT, will be misused, diverted, and/or

abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of FANAPT misuse or abuse.

Iloperidone and P88 bind to sigma receptors. Iloperidone IC50 for sigma receptors was lower than for D2 receptors and P88 IC50 for sigma receptors was in the same range as for D2 receptors. Sigma receptors are known to be involved in addiction, amnesia, pain, depression, neuroprotection and ion channel regulation.

Iloperidone and the P88 metabolite revealed higher affinity for the hERG channel than other antipsychotic agents and concentration-dependently prolonged action potential durations in dog Purkinje fibres. Although no effects on ECG were seen in dog studies, Iloperidone is considered to have a high torsadogenic potential, which constitutes a major safety risk for patients. However it is the view of the non-clinical assessor that additional non-clinical studies would not add further weight to the benefit/risk evaluation.

P88 is a major metabolite in humans where its exposure is higher than Iloperidone exposure whereas P88 levels were very low, if any, in rats and dogs. The Applicant conducted only single-dose studies in the rat and the rabbit and two genotoxicity tests (Ames and chromosomal aberrations). P88 interconverts with Iloperidone. In rats, the equilibrium of the reduction/oxidation reaction favoured Iloperidone. Iloperidone:P88 AUC ratios reached 19.1 in rats treated with Iloperidone at 16 mg/kg for 5 days, and 0.69 in humans given 12 mg Iloperidone. In these studies, P88 levels in humans were 6.8-18.6-fold higher than those in rats. Taking into account the dose levels used in toxicity studies performed with Iloperidone (48 mg/kg/day in 26-week study), conducting additional studies with Iloperidone in rats to reach human P88 levels is not viewed as feasible. Since exposure to Iloperidone is also higher than exposure to P88 in rats treated with P88 (6-9-fold at target exposure levels), performing additional toxicity studies with P88 is not considered as relevant. In rabbits, the formation of P88 from Iloperidone is one of the major biotransformation pathways of Iloperidone (iloperidone:P88 AUC ratio of 1.8 after a 5 mg/kg oral dose, study DMPK(US) R99-1190).

Considering the interconversion of Iloperidone and P88, and their similar receptor binding profile, it seems acceptable to use the sum of Iloperidone and P88 to perform exposure assessments. Additional studies are not deemed necessary to qualify P88 since it could be relied on rat/rabbit studies performed with Iloperidone to cover general toxicity, in vivo genotoxicity, and reproduction toxicity.

The results of the carcinogenicity studies are included in the proposed SmPC section 5.3.

In the embryo-fetal toxicity performed in rabbits, the incidence of foetuses with a large or displaced stomach (25%) was increased vs. both study controls (5.1%) or historical controls (12.1%) at the high dose level. Although maternotoxicity and embryolethality observed in this dose group may have been a contributing factor, the underlying mechanism is actually not established. Findings seen in this high dose group are reported in proposed SPC 5.3 (maternal toxicity, early intrauterine deaths, decreased fetal viability at term, stomach findings).

Phototoxicity has not been sufficiently investigated, and considering that the phototoxic potential of iloperidone cannot be ruled out, the inclusion of Photosafety as an Important Potential Risk in the RMP has been accepted by the Applicant.

Collectively, the significant findings from Iloperidone and P95 toxicology studies are considered pharmacologically mediated. The major target organ toxicities for Iloperidone in acute and repeated dose toxicity studies were: mammary glands (vacuolization, hyperplasia), uterus and/or vagina (altered cycling), adrenal glands (increased weight), and the thyroid (follicular hyperplasia), with additional effects on the testes and prostate at high exposures. Clinical signs and target organ toxicity were similar in the animals dosed with either Iloperidone or P95. Iloperidone and P95 were not teratogenic and

Iloperidone showed only limited effects in other reproductive toxicity studies that did not cause maternal toxicity. No significant mutagenic or carcinogenic potential was determined in studies conducted with Iloperidone. In addition, no mutagenic potential was identified with P95. P95 was associated with increased neoplasms in pituitary and pancreas because of hyperprolactinaemia, and in kidney in association with renal tubular toxicity.

From a non-clinical point of view, safety margins to human dosing obtained from non-clinical studies are still very small for a non-life-threatening indication. However, it is not considered likely that further non-clinical studies or discussion will elaborate further on the potential risks to humans from this product, but the low safety margins could be reflected upon in the overall benefit/risk profile of the product.

Several environmental fate studies are currently not finalized, but are on-going or planned and the results from these studies may trigger additional ERA studies. At this point, no final conclusions regarding the environmental risk of Iloperidone can be drawn.

2.3.6. Conclusion on the non-clinical aspects

From a non-clinical point of view, the data presented is acceptable and issues have been resolved.

A final ERA has not been agreed.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.>

- Tabular overview of clinical studies

Study Phase and Sponsor	Study Number	Number of Subjects Exposed to Study Drug	
		All Treatments (including placebo and active controls)	Treated with Iloperidone
Phase I HMR	ILBP101/101A	27	18
	ILBP102	5	5
	ILBP103	22	22
	ILPB104	16	5
	ILPB105	3	3
	ILPB106	30	30
Phase I Novartis	ILO522 0102	23	23

Study Phase and Sponsor	Study Number	Number of Subjects Exposed to Study Drug	
		All Treatments (including placebo and active controls)	Treated with Iloperidone
	ILO522 0103	16	16
Phase I Novartis	ILO522 0104	27	27
	ILO522 0105	26	26
	ILO522 0107	19	19
	ILO522 0108	23	23
	ILO522 0109	32	32
	ILO522 0110	24	24
	ILO522 0112	32	32
	ILO522A2301	6	6
	ILO522 B210	84	64
	ILO522E2101 Part C	35	35
Phase I Vanda	VP-VYV-683-1001	16	16
	VP-VYV-683-1002	24	24
Phase II HMR	ILBP199	14	5
	ILPB200	18	15
	ILPB201	38	31
	ILPB202	104	69
	ILPB203	24	24
	ILPB205	15	12
	ILPB303	9	6
Phase II Novartis	ILP2001	120	95
	ILO522 2328	180	106
Phase III Novartis	ILP3000	610	393
	ILP3001	597	452
	ILP3002	553	417
	ILP3003	484	362
	ILP3004	613	367
	ILP3005	689	378
	ILP3007[a]	130	78
Phase III Vanda	VP-VYV-683-3101	597	300
Phase IIIb Novartis	ILO522D2301	635	635
Phase IV Novartis	ILO522D2401	32	32

Study Phase and Sponsor	Study Number	Number of Subjects Exposed to Study Drug	
		All Treatments (including placebo and active controls)	Treated with Iloperidone
	ILO522DUS01	500	500

- [a]Study in elderly patients with dementia.

Pharmacokinetics

Absorption

After oral administration, Iloperidone was absorbed with a t_{max} of approximately 2 hours. The extent of absorption is unknown because an absolute bioavailability study has not been conducted. However, the absolute bioavailability has been estimated to about 36% in CYP2D6 extensive metabolisers and about 54% in CYP2D6 poor metabolisers.

Some capsule and tablet formulations were used in the very early clinical studies, but these were not used subsequently. The key bioequivalence study is Study ILO522 0110 which demonstrated that the final to-be-marketed tablet form (FMF-T) was bioequivalent to the capsule formulations CSF-C and FMF-C with respect to Iloperidone and its major metabolites. These three formulations (FMT-T, CSF-C and FMF-C) were used in all later studies, including all Phase 3 studies.

Since an over-encapsulated version of FMT-T was used in some clinical studies, a bioequivalence study comparing the naked tablets with the over-encapsulated version was carried out (Study VP-VYV-683-1002). The study, which was done under fed conditions, showed bioequivalence with regard to AUC, but the 90% CI for the C_{max} ratio was slightly outside the 80-125% interval. However, this finding is not considered clinically significant.

Food prolongs t_{max} of Iloperidone with about one hour compared to the fasted state. It also appears to increase AUC, but the increase is small and not clinically relevant. Please see Table 2 (data from Study ILO522 0105, food effect study).

Table 2 – Pharmacokinetic parameters of Iloperidone, P88 and P95 following a single 3 mg dose (3 x 1 mg tablets) under fasted and fed conditions

Analyte	Parameter	3 X 1 mg tablets (fasted)	3 x 1 mg tablets (fed)
Iloperidone	AUC_{0-t} (ng.h/mL)	39.9 ± 17.7	42.4 ± 17.0
	$AUC_{0-\infty}$ (ng.h/mL)	44.4 ± 19.7	47.5 ± 19.1
	C_{max} (ng/mL)	3.3 ± 1.5	2.8 ± 0.8
	T_{max} (h)*	2	3
	$t_{1/2}$ (h)	25 ± 10	23.5 ± 5.8
P88	AUC_{0-t} (ng.h/mL)	64.1± 20.7	66.4 ± 17.6
	$AUC_{0-\infty}$ (ng.h/mL)	71.8 ± 24.4	74.5 ± 21.2
	C_{max} (ng/mL)	2.9 ± 0.8	2.7 ± 0.5
	T_{max} (h)*	4	6
	$t_{1/2}$ (h)	21.4 ± 6.0	20.7 ± 5.6
P95	AUC_{0-t} (ng.h/mL)	116.4 ± 47.4	105.3 ± 42.2
	$AUC_{0-\infty}$ (ng.h/mL)	130.9 ± 52.1	121.7 ± 48.2
	C_{max} (ng/mL)	3.6 ± 1.8	2.9 ± 1.4
	T_{max} (h)*	6	12
	$t_{1/2}$ (h)	21.4 ± 5.7	22.8 ± 6.2

*= median

Distribution

The apparent volume of distribution (V_z/F) for Iloperidone is approximately 1500-3000 L. Even when considering the oral bioavailability, this suggests a large volume of distribution and hence a high affinity to extravascular tissues.

The plasma protein binding of Iloperidone and major metabolites is high (about 95%).

Metabolism and Elimination

Following single dose, the total apparent oral clearance was 50-200 L/h, and the terminal elimination half-life was 10-30 h, with poor CYP2D6 metabolisers showing longer t1/2 than extensive metabolizers.

Iloperidone is primarily metabolised, and excretion of unchanged Iloperidone is minimal. Iloperidone is metabolised via several pathways: 1) Carbonyl reduction resulting in the metabolite P88; 2) O-demethylation mediated by CYP3A4 resulting in the metabolite P89; 3) Oxidation mediated by CYP2D6 resulting in the metabolite P94 which undergoes further oxidation and decarboxylation to form the metabolite P95. Please see **Figure 2**. Additional steps lead to further metabolites, and excreted metabolites are highly conjugated as glucuronides or sulfates. Metabolites are excreted mainly via the renal route.

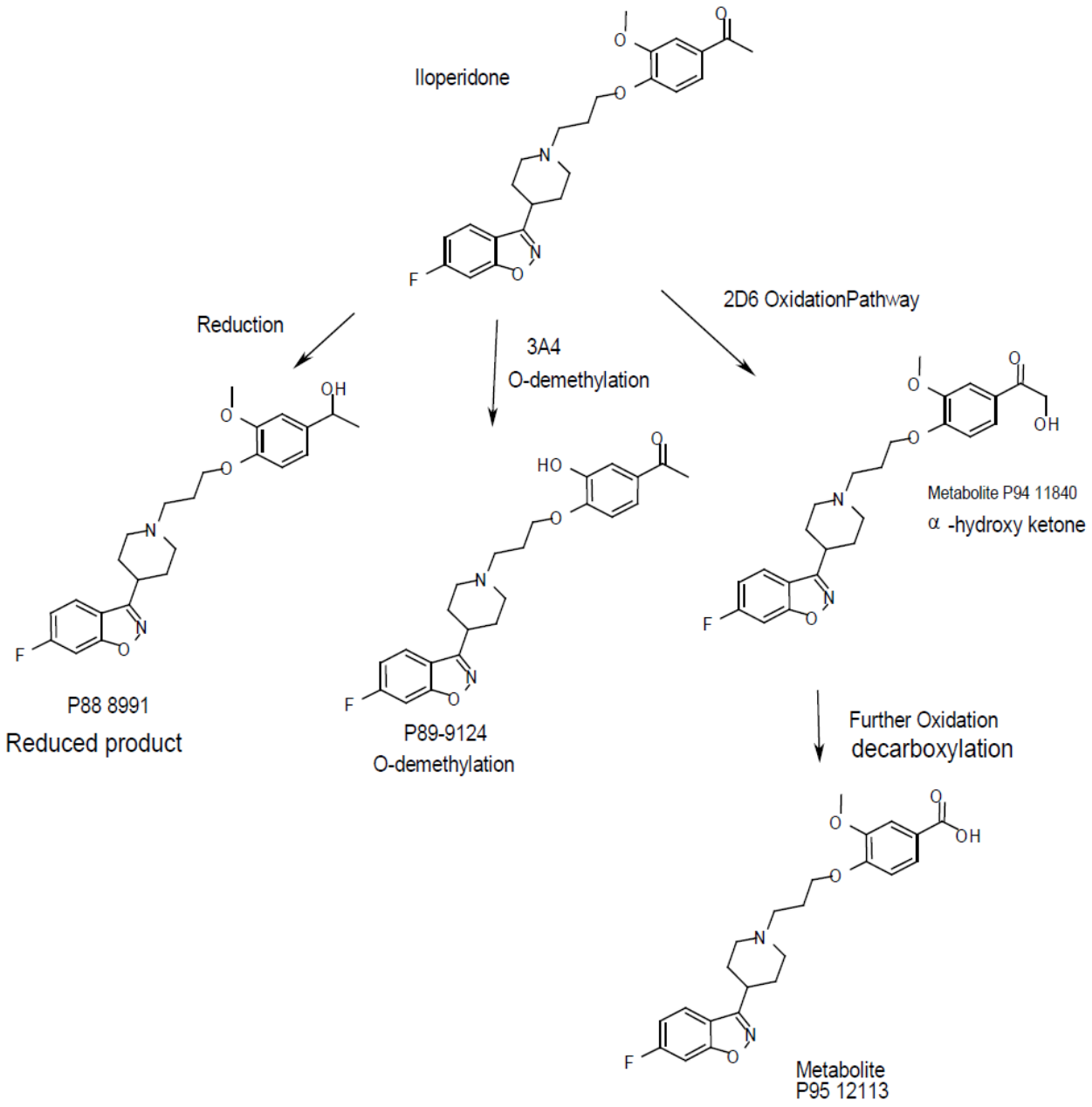

Figure 2 – Metabolic pathway of iloperidone of practical importance in humans

The predominant metabolites are P95 and P88. At steady state, the exposure of P95 is more than double the exposure of Iloperidone, but P95 has low affinity for monoamine receptors and does not penetrate the blood-brain barrier. The exposure of P88 is moderately higher than the exposure of Iloperidone, and P88 has similar pharmacological activity to that of Iloperidone. P89 is only present in small concentrations.

The fact that Iloperidone is substrate for CYP2D6 results in a significantly higher exposure of Iloperidone (1.5-fold) and P88 (2-fold) in CYP2D6 poor metabolisers compared to CYP2D6 extensive metabolisers. See Table 3 and Table 4 below (data from Study ILO522 0104).

Table 3 – Mean (CV%) iloperidone pharmacokinetic parameters in extensive and poor CYP2D6 metabolizers following a 3 mg single oral dose of iloperidone

Iloperidone PK Parameters	Mean (CV%)		
	Extensive (N=18)	Poor (N=8)	% Difference [a]
t_{max} (h) [b]	2.5 (2-3)	3 (1-4)	--
C_{max} (ng/mL)	2.79 (27)	2.26 (13)	-19.0
$AUC_{0-\infty}$ (ng*hr/mL)	29.4 (36)	46.3 (17)	57.4
$t_{½}$ (h)	17.6 (36)	32.8 (21)	88.3
CL_T/F (L/hr)	116.5 (39)	66.4 (16)	-43.0
V_Z/F (L)	2,868 (49)	3,095 (19)	7.9
Ae (% of dose)	0.45 (69)	0.70 (34)	35.7
CL_R (mL/min)	8.2 (56)	9.28 (25)	13.1

[a] % Difference = [(Poor-Extensive)/Extensive]*100
[b] Median (Range)

Table 4 – Mean (CV%) P88 pharmacokinetic parameters in extensive and poor CYP2D6 metabolizers following a 3 mg single oral dose of iloperidone

P88 PK Parameters	Mean (CV%)		
	Extensive (N=18)	Poor (N=8)	% Difference [a]
t_{max} (h) [b]	4.0 (3-6)	4.5 (3-6)	--
C_{max} (ng/mL)	2.32 (30)	3.33 (20)	43.5
$AUC_{0-\infty}$ (ng*hr/mL)	49.4 (43)	96.4 (21)	95.1
$t_{½}$ (h)	25.5 (45)	37.3 (20)	46.3
CL_T/F (L/hr)	68.7 (32)	32.3 (20)	-53.0
V_Z/F (L)	2,343 (45)	1,715 (21)	-26.8
Ae (% of dose)	4.2 (57)	8.0 (30)	90.5
CL_R (mL/min)	46.5 (35)	51.3 (16)	10.3

[a] % Difference = [(Poor-Extensive)/Extensive]*100
[b] Median (Range)

In the dose range from 2 mg b.i.d. to 8 mg b.i.d., dose-proportionality appears to be present. However, at higher doses, a higher than proportional increase in exposure must be expected. Please see to Table 5 (data from Study ILO522 0112).

Table 5 – Mean (CV%) iloperidone pharmacokinetic parameters in schizophrenic patients following multiple oral dose of iloperidone

Parameters	Mean (CV%)			
	2.0 mg	4.0 mg	8.0 mg	12.0 mg
t_{max}^{ss} (h)*	1.8 (62)	1.5 (35)	1.5 (44)	1.5 (32)
C_{max}^{ss} (ng/mL)	4.12 (58)	8.87 (53)	18.93 (45)	32.14 (43)
C_{min}^{ss} (ng/mL)	1.31 (62)	2.93 (74)	6.92 (63)	11.21 (62)
AUC_t (ng•h/ml)	29.96 (63)	64.84 (66)	133.1 (52)	231.9 (48)
C_{avg}^{ss} (ng/mL)	2.50 (63)	5.40 (66)	11.09 (52)	19.33(48)
N	28	24	20	16

*Median range

Dose proportionality and time dependencies

Special populations

There are no indications that the pharmacokinetics of Iloperidone in patients with schizophrenia is markedly different when compared to healthy subjects.

With respect to special populations, the Applicant has addressed patients with impaired renal function, patients with impaired hepatic function, as well as the effect of gender, race, body weight and age.

In Study ILO522 0102, where patients with severe renal impairment were compared to matched healthy subjects, severe renal impairment appeared to be associated with an about 80% increase in Iloperidone exposure (expressed as $AUC_{0-\infty}$) and a 3-fold increase in P95 exposure.

Patients with mild or moderate renal impairment have not been specifically studied, although the population pharmacokinetic analysis did not indicate that the exposure to Iloperidone and its major metabolites was affected by renal function in the range of creatinine clearance values from 50-200 ml/min.

With regard to hepatic impairment, Iloperidone has not been studied in patients with severe hepatic impairment.

Two studies (ILO522 0103 and IL0522 D2401) investigated patients with mild and moderate hepatic impairment. However, a distinction between mildly and moderately impaired patients has only been made for the latter study. It appears that exposure to particularly P88 but also to P95 is markedly higher in patients with moderate hepatic impairment compared to normal subjects, especially when looking at free drug plasma concentrations. Please refer to Table 6, which presents free drug plasma concentrations from Study IL0522 D2401.

Table 6 – Pharmacokinetic parameters of iloperidone and the metabolites P88 and P95 based on free drug in plasma

Metabolite	Parameter	Normal Function	Mild impairment	Moderate impairment
Iloperidone	Cmax,u (ng/mL)	0.0489 ± 0.0228	0.0491 ± 0.0257	0.0495 ± 0.0117
	AUClast,u (ng.h/mL)	0.743 ± 0.305	0.645 ± 0.300	0.824 ± 0.370
	AUCinf,u (ng.h/mL)	0.878 ± 0.301	0.712 ± 0.328	0.815 ± 0.266
P88	Cmax,u (ng/mL)	0.109 ± 0.0443	0.106 ± 0.0544	0.181 ± 0.101
	AUClast,u (ng.h/mL)	3.51 ± 1.24	3.11 ± 1.46	6.31 ± 4.92
	AUCinf,u (ng.h/mL)	3.72 ± 1.36	3.21 ± 1.62	7.44 ± 5.98
P95	Cmax,u (ng/mL)	0.193 ± 0.0730	0.209 ± 0.0784	0.198 ± 0.168
	AUClast,u (ng.h/mL)	7.94 ± 2.54	8.16 ± 2.01	9.14 ± 6.13
	AUCinf,u (ng.h/mL)	9.61 ± 2.38	9.78 ± 0.931	14.9 ± 6.04

Values are mean ± sd.

Regarding gender effects, exposure is markedly higher in women compared to men – even after having adjusted for body size.

The analyses presented have not showed any differences in pharmacokinetics by race.

The effect of weight on the pharmacokinetics of Iloperidone is minor.

The effect of age on the pharmacokinetics of Iloperidone has not been investigated in dedicated studies.

For children, no pharmacokinetic data are available. The proposed indication only encompasses adults.

The P450 isozymes CYP2D6 and CYP3A4 have *in vivo* been shown to be of key relevance for the elimination of Iloperidone and to be involved in clinically relevant increases in exposure to Iloperidone and P88 when Iloperidone is administered concomitantly with inhibitors of these enzymes.

2.4.2. Pharmacodynamics

Mechanism of action

Iloperidone is a piperidinyl benzisoxazole derivative developed for treatment of the symptoms of schizophrenia. It acts as antagonist at dopaminergic, serotonergic and adrenergic receptors having affinity to dopaminergic D_2 and D_3 receptors, serotonergic 5-HT_{1a} and 5-HT_{2a}, and adrenergic α_1 and α_{2c} receptors.

Primary and Secondary pharmacology

The pharmacological profile of Iloperidone is consistent with one of a second-generation antipsychotic.

The conducted analyses of the relationship between Iloperidone and P88 concentrations and QTc unequivocally show that QTc increases with increasing concentrations of Iloperidone and P88.

The relationship between efficacy as expressed by for example PANSS Total Score and Iloperidone exposure was not straightforward in all analyses. The relationship was clearer for the active metabolite, P88.

2.4.3. Discussion on clinical pharmacology

The applied bioanalytical, pharmacokinetic and statistical methods are overall acceptable. During the clinical development encompassing several sponsors, a number of different formulations have been used. The submitted documents are not very clear in outlining exactly which formulation was used in the various clinical studies. However, the bioequivalence links between the various formulations are overall acceptable.

The recommendation that Iloperidone can be taken without regard to food is supported.

With regard to elimination, Study ILO522 D2401 had an unusually high terminal half-life for healthy subjects, which is explained by a longer sampling time and a more sensitive assay as compared to other studies.

The significant effect of CYP2D6 poor metaboliser status warrants genotyping with regard to CYP2D6 and dose adjustments in patients who are poor metabolisers. However, CYP2D6 genotyping may not be feasible in all contexts due to the availability, as mentioned by the ad hoc expert group.

In the SmPC, the maximum recommended target dose for CYP2D6 poor metabolisers is 6 mg twice daily (12 mg/day). This dose recommendation is made solely from a safety perspective due to the risk of QTc prolongation which is correlated to plasma concentration. This is increased in patients who are poor metabolisers. In addition, the dose should be decreased to 4 mg b.i.d. in the maintenance phase. The recommended dose has not been shown to be effective in short term clinical trials. Thus, the recommended dose is questioned The need for lower dosage increments in patients who are CYP2D6 poor metabolisers have not been discussed by the Applicant as requested. The half-life is significant longer in this patient population which could lead to, in particular, an increased risk of AE related to alpha adrenergic blockage.,. Moreover, since a systematic identification of CYP2D6 status is not done routinely, one should consider any patient as a poor CYP2D6 metabolizer. A treatment regimen shown to be more effective than placebo would most likely require a dose of more than 6 mg b.i.d. Please refer to the discussion on Clinical Efficacy. If this is not possible (genotype unknown or the patient is a poor metaboliser), the patient will be at risk of insufficient treatment of psychotic symptoms, or in a stable patient, the recurrence of psychotic symptoms. On the other hand, if there are no recommendations concerning genotype, it could lead to the treatment with 12 mg b.i.d. in patients who are CYP2D6 poor metabolisers with the increased risk of significant QTc prolongation and arrhythmia.

Given the clear relationship between QTc prolongation and exposure, CYP2D6 poor metaboliser status and treatment with strong inhibitors of CYP3A4 and CYP2D6 are risk factors for QTc prolongation. Strong CYP3A4 inhibitors might be harmful and should be strongly discouraged, as their co-administration could result in a tripling exposure of the drug in particular when administered in patients who are CYP2D6 poor metabolisers or patients concomitantly treated with strong CYP2D6 inhibitors. However, it is currently unknown if Iloperidone can be safely administered with weak and/or moderate inhibitors of CYP2D6 and/or CYP3A4 considering that the observed QTc prolongation is closely linked to the plasma concentration. It is likely that at least the combination of treatment with a moderate CYP3A4 inhibitor in a CYP2D6 poor metaboliser or concomitantly treatment with a strong CYP2D6 inhibitor will lead to clinically relevant increases in plasma concentration that could lead to a clinically relevant QTc prolongation. The scenario is similar when using a moderate CYP2D6 inhibitor with a strong CYP3A4 inhibitor. It is unknown whether even the addition of a mild inhibitor co-administered with a strong inhibitor will lead to a clinically relevant QTc prolongation. The co-administration of two moderate inhibitors might also lead to a clinically relevant increase in plasma concentration and thus increase the risk of QTc prolongation. This uncertainty would mean that, from a precautionary approach, the patients cannot be treated with a number of medicines if not subjected to simultaneous extensive ECG monitoring.

No discussion about time dependency has been presented by the Applicant. From a number of studies, it appears that steady state concentrations of Iloperidone and its major metabolites were obtained not later than after one week. This is in line with the single dose pharmacokinetics.

Between subject CV% for PK parameters is between 25 and 50% while within subject variability is about 12-20 CV%.

Severe renal impairment appeared to be associated with an about 80% increase in Iloperidone exposure (expressed as $AUC_{0-\infty}$) and a 3-fold increase in P95 exposure. The disposition profiles of the metabolite P95-12113 showed higher exposure and lower clearance in renally impaired subjects. This was evident by sustained higher plasma concentrations of this metabolite. These results suggest that P95-12113 could accumulate upon chronic dosing of Iloperidone. As P95-12113 can bind to alpha-1-adrenergic receptors, patients with severe renal impairment may be more likely to experience effects of alpha-1-adrenoreceptor blockage than those with normal renal function. Overall, there are uncertainties about the safety of Iloperidone in patients with impaired renal function that warrant a non-recommendation for patients with severe renal impairment and a cautionary statement for patients with moderate renal impairment in the SmPC.

With regard to hepatic impairment, Iloperidone has not been studied in patients with severe hepatic impairment, and therefore the proposed non-recommendation for this population in the SmPC is supported.

Regarding gender effects, exposure is markedly higher in women compared to men – even after having adjusted for body size. Data from two healthy volunteer studies did not suggest such differences, but these were small studies using low doses of Iloperidone, which might not fully reflect the proposed posology. However, there was no gender difference with regard to AE in safety group 2 (double blind, placebo controlled studies). This indicates that the possible exposure difference does not translate into an increased risk of AE.

The PoP-PK analysis did not allow for a detection of ethnic differences; this is not surprising as the polymorphism of CYP2D6 varies substantially, and some ethnicities were only included in a minor number. The proposed wording regarding frequencies of CYP2D6 poor metabolisers different races have been included in the SmPC.

With regard to the effect of age, there is no PK data available in patients 65 years and older. The presentation on *in vitro* findings of relevance for potential drug-drug interactions in the Summary of Clinical Pharmacology Studies is very short. Additional clarification indicates that Iloperidone and P88 and P95 are not substrates for any of the transporters studied, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, or MATE2-K. The dextrometorphan interaction study (ILO522 0104) study was conducted with an Iloperidone dose of 3 mg. The DDI study using midazolam as a CYP3A4 biomarker suggest that Iloperidone is a weak inhibitor of CYP3A4 at doses up to 10 mg twice daily. Point ratio estimates of midazolam AUC exposures were below 1.5 with upper 90% CI less than 2. These findings are consistent with the status as a weak CYP3A4 inhibitor and unlikely to be of general clinical relevance.

A comparison of actual drug concentrations in medically treated patients to the in vitro IC50 values for specific CYP inhibition show that therapeutic concentrations are 10 to 30-fold lower than the lowest IC50 values estimated.

The P450 isozymes CYP2D6 and CYP3A4 are of key relevance for the elimination of Iloperidone and are involved in clinically relevant increases in exposure to Iloperidone and P88 when Iloperidone is administered concomitantly with inhibitors of these enzymes. The drug-drug interaction trial with fluoxetine shows that inhibition of both CYP2D6 and CYP3A4 or inhibition of CYP3A4 combined with CYP2D6 slow metaboliser status could result in more than a doubling of Iloperidone and P88 exposure.

Consequently, the proposed dose reduction in these patients may not be sufficient, and one may question if treatment with Iloperidone is at all advisable. This is not sufficiently reflected in the SmPC.

The Applicant provided clarification regarding *in vivo* findings related to the P-glycoprotein interaction but only regarding the renal part. No discussion on the lack of study investigating the inhibition of a P-gp substrate on the intestinal part, notably as dabigatran absorption is located at the GI tract have been provided. Iloperidone should be used with caution concomitantly with drugs that are substrates of p-gp and has a bioavailability <80%, and a narrow therapeutic window.

P88 appears to have a similar receptor affinity profile as do the parent compound, and there is some interconversion between these two molecules as well. The P95 metabolite is the most abundant and as it does not penetrate the blood-brain barrier to a meaningful extent, this metabolite is unlikely to contribute to the pharmacodynamic efficacy of Iloperidone but could contribute the non-CNS adverse events observed. The conducted analyses show that QTc increases with increasing concentrations of Iloperidone and P88. The Applicant claims that the effect appears to plateau within the investigated concentration range. However, this claim appears to be based on very few data points and is consequently not well substantiated.

No discussion for risk of pharmacodynamic interaction with other QTc-prolonging medicines and the feasibility of handling this in a real-world setting has been provided.

2.4.4. Conclusions on clinical pharmacology

The recommended dose is questioned in patients who are CYP2D6 poor metabolisers or with an unknown genotype. It is currently unknown if Iloperidone can be safely administered with weak and/or moderate inhibitors of CYP2D6 and/or CYP3A4 considering that the observed QTc prolongation is closely linked to the plasma concentration.

2.5. Clinical efficacy

2.5.1. Dose response studies and main clinical studies

No formal dose-response studies were performed prior to the Phase 3 studies where doses between 4 and 24 mg/d were studied. The dose response relationship was mainly supported through the short-term clinical trials, in particular studies 3101, 3005, and to a lesser extent studies ILPB202 and 3004. Afterwards, dosing recommendations were evaluated/confirmed within the development of PK-PD models based on data from the short-term trials 3000, 3005 and study 3101. CILO522D2301 study results serve as primary source for dosing recommendations for maintenance treatment.

The Applicant has claimed that five placebo-controlled studies addressing short-term efficacy serve as the primary source of efficacy data. These are:

- VP-VYV-683-3101 (3101), a Phase 3 study conducted by Vanda;
- ILP3000 (3000), ILP3004 (3004), ILP3005 (3005), three Phase 3 studies conducted by Novartis;
- ILPB202 (B202), a Phase 2 study conducted by Hoechst-Marion-Roussel (HMR);

In addition, to support long-term persistence of efficacy the Applicant has submitted the results of the pivotal clinical study CILO522D2301 (D2301).

The B202 study did according to the Applicant's Clinical Summary not meet the protocol-defined primary endpoint. Nor did the phase 3 studies 3000 and 3005, and these studies are by the Applicant considered negative studies for regulatory purposes. The studies B202, 3000 and 3005 are therefore described under the section "Supportive studies" together with other studies that the Applicant has claimed as supportive studies. Thus, remaining as main clinical studies are study nos. 3101 (for short-term efficacy), 3004 (for short-term efficacy), and CIL0522D2301 (long-term efficacy).

Short-term efficacy

Clinical study VP-VV-683-3101, hereafter referred to as study 3101. Title of Study: A Randomized, Double-Blind, Placebo- and Ziprasidone-Controlled, Multicenter Study to Evaluate the Efficacy, Safety and Tolerability of a 24 mg/day Dose Iloperidone Given b.i.d.for 28 Days to Schizophrenic Patients in Acute Exacerbation Followed by a Long-Term Treatment Phase

This was a randomized, double-blind, placebo- and ziprasidone-controlled, parallel-group, multicenter study to evaluate the efficacy and safety of fixed doses of iloperidone and ziprasidone in patients with schizophrenia. This study had 3 phases: the pre-randomization; short-term, double-blind; and long-term, open-label phase. The pre-randomization phase consisted of a screening period (Days -14 to -3) and a baseline period (Day 0). The 4-week, short-term, double-blind phase consisted of a 7-day fixed titration period (Days 1 to 7) followed by a fixed-dosage maintenance period (Days 8 to 28). The iloperidone maintenance dose was 24 mg/d (b.i.d.) and for ziprasidone 160 mg/d. The primary efficacy variable was the change from baseline to endpoint (Day 28 or early termination) in the PANSS-T score in the modified ITT population (patients who received at least one dose of study medication and had at least one post-baseline efficacy measurement). Based on the primary analysis, the MMRM model with baseline as covariate, a statistically significantly greater improvement from baseline in PANSS-T score was demonstrated by the iloperidone group compared with the placebo group at Day 28 (–12.01 at Day 28, $P < 0.01$ compared with placebo). The iloperidone group also exhibited a statistically significantly greater improvement from baseline in PANSS-T score compared with the placebo group using the LOCF dataset. No impressive numerical efficacy differences were seen between iloperidone and ziprasidone, nor in the number of secondary endpoints met. The onset of action appeared to occur later with iloperidone than with ziprasidone.

Clinical study ILP 3004, hereafter referred to as study 3004. Study title: A randomized, double-blind, placebo- and risperidone-controlled, multicenter study to evaluate the efficacy and safety of two non-overlapping dose ranges of iloperidone given b.i.d. for 42 days to schizophrenic patients with acute or subacute exacerbation, followed by a risperidone controlled, long-term treatment phase with iloperidone given q.d.

The short-term efficacy part of this study in patients with schizophrenia and schizoaffective disorder had a pre-randomization phase, consisting of a screening period (Days -30 to -3) and a single-blind placebo run-in period (Days –2 to 0). This was followed by a double-blind phase (6 weeks; Days 1-42) consisting of fixed titration (Days 1-7) and flexible dosage maintenance (Days 8-42) periods. Patients were randomized in a ratio of 1:1:1:1 to receive maintenance treatment with either iloperidone 4-8 mg/d, iloperidone 10-16 mg/d, risperidone 4-8 mg/d or placebo. The study medication was administered b.i.d. The primary efficacy variable was the change from baseline to endpoint (Day 42 or early termination) in the PANSS-derived BPRS score in the modified ITT population (patients who received at least one dose of study medication and had at least one post-baseline efficacy measurement) with LOCF imputation for missing data. In order to control for multiplicity in the analysis of efficacy, the primary comparison was between the iloperidone 10-16 mg/d group and the placebo group. If this test was significant at the 0.05 level, the subsequent pairwise comparison of the iloperidone 4-8 mg/d group with placebo would be considered significant at the 0.05 level. For the LOCF dataset, there was a statistically significant

reduction in the primary endpoint PANSS-derived BPRS score for both iloperidone treatment groups compared to the placebo group at Week 6 (p=0.012 and 0.001 for the iloperidone 4-8 mg/d and 10-16 mg/d groups, respectively). Numerically, the effect size favoured the 10-16 mg/d group. The effect size was numerically higher in the risperidone group than in the two iloperidone groups. Also in this study, the onset of action appeared to occur later with iloperidone than with risperidone. A subgroup post-hoc analysis was conducted to characterize the potential differences between schizophrenic and schizoaffective patients, and the potential impact of the differences on the analysis for the primary outcome. This analysis failed to reach the statistical requirement in patients with schizophrenia.

Long-term efficacy

Clinical study CILO522D2301, hereafter referred to as study 2301. Title of Study: A multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate prevention of relapse in patients with schizophrenia receiving either flexible dose iloperidone or placebo in long-term use (up to 26 weeks) followed by up to 52 weeks of open-label extension Phase

This was a multicenter, double-blind, placebo-controlled, parallel-group, randomized withdrawal study to determine the efficacy of flexible dosing of iloperidone (8-24 mg/day total daily dose) given as a twice daily regimen compared with placebo in preventing relapse or impending relapse in long-term use (up to 26 weeks) in patients with schizophrenia as measured by the time to first psychiatric relapse or impending relapse. The study consisted of a Screening phase, an open-label Titration phase, an open-label Stabilization phase, and a Double-Blind Relapse Prevention phase. The primary efficacy analysis of time to relapse or impending relapse was the log rank test in which the hazard functions of placebo and iloperidone were compared in a relative manner. A Cox regression model was also used to provide an estimated hazard ratio. The Full Analysis set (FAS) was all randomized patients who received at least 1 dose of double-blind study drug and for whom at least one efficacy measurement was obtained while on study drug during the DBRP phase. The efficacy analyses were based on the FAS population and supplemented by a per-protocol analysis. The primary endpoint was met both for the FAS population and in the per-protocol analysis.

The following tables summarise the efficacy results from the three main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 7 - Summary of efficacy for trial 3101

Title: A Randomized, Double-Blind, Placebo- and Ziprasidone-Controlled, Multicenter Study to Evaluate the Efficacy, Safety and Tolerability of a 24 mg/day Dose Iloperidone Given b.i.d. for 28 Days to Schizophrenic Patients in Acute Exacerbation Followed by a Long-Term Treatment Phase.		
Study identifier	VP-VYV-683-3101	
Design	Prospective, randomized, double-blind, placebo- and ziprasidone-controlled, parallelgroup, multicenter study.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	4 weeks of double blind treatment: -Fixed titration period (Days 1-7). -Flexible dosage maintenance period (Days 8-28) - Pre-randomization phase/Screening period (Days -14 to -3) -Optional open-label phase for up to 175 days.
Hypothesis	Superiority of the iloperidone 24 mg/d compared to placebo Superiority of the iloperidone 24 mg/d in iloperidone-treated CNTF (-) patients compared to placebo CNTF (-) patients	
Treatments groups	iloperidone 24 mg/d	Oral capsule. 6 weeks, 283 randomized patients
	ziprasidone 160 mg/d	Oral capsule. 6 weeks, 144 randomized patients

	Placebo		Oral capsule. 6 weeks, 140 randomized patients
Endpoints and definitions	Primary endpoint (MMRM, mITT)	PANSS-T	Change from baseline to endpoint (Day 28 or premature discontinuation) on the comparison between Ilo 24 mg/d group and placebo, and between the iloperidone 24 mg/d CNTF FS63Ter(-) genotype group and placebo if the iloperidone 24 mg/d comparison with placebo was statistically significant, MMRM, mITT.
	Secondary endpoints (MMRM, mITT)	1.BPRS 2.PANSS-N 3.PANSS-P	The change from baseline to each post-baseline assessment in the scores of the PANSS subscales (PANSS-P, PANSS-N, and PANSS-GP), the PANSS-derived 18-item BPRS score, ITT, LOCF.
		4. CGI-S	The change from baseline on the CGI-S at each time point.
		5. Proportion of responders (with 20% or greater reduction)	The proportion of patients achieving clinical improvement (defined as minimally, much, or very much improved) on the PANSS-T at each time point.

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Primary analysis was based on the MMRM dataset using an ANCOVA model (including treatment, center, baseline, and the treatment-by baseline) Additional analysis was based on LOCF and OC. Time point: 4 weeks of treatment.			
PANSS-T change from Baseline to endpoint (Day 28/MMRM), ANCOVA, mITT.	Treatment group	Ilo 24 md/d	Zipra 160 md/d	Placebo
	Number of subject	283	144	140
	Point estimate	Week 4		
	Adj. Mean Change	-12.01	-12.27	-7.08
	Treatment differences			
		Ilo 24 md/d vs. pbo	Zipra 160 md/d vs. pbo	Placebo
	LS Mean	**1.80**	2.06	
	95% CI	**[-8.47, -1.38]**	[-9.23, -1.14]	
	p-value	**0.006***	0.012*	
PANSS-T change from Baseline to endpoint CNTF FS63Ter(-) genotype group (Day 28/MMRM), ANCOVA, mITT.	Treatment group	**Ilo 24 md/d CNTF(-)**	Ilo 24 md/d CNTF(+)	Placebo CNTF(-)
	Number of subject	**218**	61	107
	Adj. Mean Change	**-12.5**	-12.16	-5.68
	Treatment differences			
		Ilo 24 md/d CNTF(-) vs Placebo CNTF(-)	Ilo 24 md/d CNTF(-) vs Ilo 24 md/d CNTF(+)	
	Adj Change	**-6.37**	0.11	

	LS Mean	**2.05**	2.51	
	95% CI	**[-10.39, -2.34]**	[-4.82, 5.04]	
	p-value	**0.006***	0.965	
Note	For the PANSS mean change, the differences between adjusted mean change were statistically significant in favour of both iloperidone overall and CNTF(-) population compared to placebo in overall and CNTF(-) patient groups,			
Analysis description	**Secondary Analysis**			
BPRS change from Baseline to endpoint Day 28/MMRM), ANCOVA, mITT	Treatment group	Ilo 24 md/d	Zipra 160 md/d	Placebo
	Adj. Change	-7.39	-7.21	-4.62
	Treatment differences			
	LS Mean (SE)	-2.77	-2.59	
	95% CI	[-4.95, -0.59]	[-5.08, -0.09]	
	p-value	0.013*	0.042*	
(%) Proportion of responders with 20% or greater reduction for PANSS-T,mITT, LOCF	Adj. Change	45.2	45.8	37.1
	Treatment differences			
	LS Mean (SE)	8.09	8.69	
	95% CI	[-4.95, -0.59]	[-5.08, -0.09]	
	p-value	0.126	0.200	
PANSS-P change from Baseline to endpoint (Day 42/LOCF), ANCOVA, mITT, MMRM	Adj. Change	-4.21	-4.23	-2.22
	Treatment differences			
	LS Mean (SE)	-1.99	-2.01	
	95% CI	[-3.17, -0.82]	[-3.34, -0.67]	
	p-value	<0.001*	0.003*	
PANSS-N change from Baseline to endpoint (Day 42/LOCF), ANCOVA, mITT, MMRM	Adj. Change	-2.96	-3.06	-1.91
	Treatment differences			
	LS Mean (SE)	-1.05	-1.14	
	95% CI	[-1.98, -0.11]	[-2.21, -0.07]	
	p-value	0.027	0.036	
CGI-S change from baseline, (Day 42/LOCF), ANCOVA, ITT, MMRM	Adj. Change	-0.65	-0.67	-0.39
	Treatment differences			
	LS Mean (SE)	-0.26	-0.27	
	95% CI	[-0.45, -0.07]	[-0.49, -0.06]	
	p-value	0.007	0.013	

Notes	-For the BPRS score, compared with placebo, the differences was statistically significant in favour of iloperidone. (The difference was also statistically significant between CNTF (-) iloperidone patients compared to CNTF (-) placebo patients). -For the PANSS-P score, compared with placebo, the differences was statistically significant in favour of iloperidone at study endpoint (The difference was also statistically significant between CNTF (-) iloperidone patients compared to CNTF (-) placebo patients). -For the PANSS-N score, the differences was statistically significant in favour of iloperidone at Day 28, compared with placebo (on the MMRM analysis). (The difference was also statistically significant between CNTF (-) iloperidone patients compared to CNTF (-) placebo patients). -For the CGI-S score, compared with placebo, the differences was statistically significant in favour of iloperidone at Day 28 (on the MMRM analysis). (The difference was also statistically significant between CNTF (-) iloperidone patients compared to CNTF (-) placebo patients).

Table 8 - Summary of efficacy for trial 3004

Title: A randomized, double-blind, placebo- and risperidone-controlled, multicenter study to evaluate the efficacy and safety of two non-overlapping dose ranges of iloperidone given b.i.d. for 42 days to schizophrenic and schizoaffective patients, followed by a risperidonecontrolled, long-term treatment phase with iloperidone given q.d.			
Study identifier	ILO522 3004		
Design	Phase III, prospective, randomized, double-blind, placebo- and active-controlled (Risperidone), multicenter study.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		6 weeks of double blind treatment: -Fixed titration (Days 1-7) period -Flexible dosage maintenance (Days 8-42) period - Pre-randomization phase/Screening period (D -30 to -D3) -Single-blind placebo run-in period (D –2 to 0) -Long-term double-blind phase (Days 43-182), followed by a long-term double-blind extension (Days 183 to 364). -Long-term open-label extension (Days 365-onwards).
Hypothesis	Superiority of the iloperidone 10-16 mg/d group and placebo, and between the iloperidone 4-8 mg/d group and placebo if the iloperidone 10-16 mg/d comparison with placebo was statistically significant		
Treatments groups	iloperidone 4-8 mg/d		Oral capsule. 6 weeks, 153 randomized patients
	iloperidone 10-16 mg/d		Oral capsule. 6 weeks, 154 randomized patients
	risperidone 4- 8 mg/d		Oral capsule. 6 weeks, 153 randomized patients
	Placebo		Oral capsule. 6 weeks, 156 randomized patients
Endpoints and definitions	Primary endpoint	BPRS	Change from baseline to endpoint (Day 42 or premature discontinuation) on the comparison between Ilo 10-16 mg/d group and placebo, and between the iloperidone 4-8 mg/d group and placebo if the first comparison is statistically significant, ITT, LOCF, ANCOVA model
	Secondary endpoints	1.PANSS-T 2.PANSS-N 3.PANSS-P 4.PANSS-GP	The change from baseline to each post-baseline assessment in the scores of the PANSS subscales (PANSS-P, PANSS-N, and PANSS-GP), the PANSS-derived 18-item BPRS score, ITT, LOCF.

		5. CGI-C 6. CGI-S	The proportion of patients achieving a score of "improved", "much improved" or "very much improved" on the CGI-C at each timepoint The change from baseline on the CGI-S at each time point.
		7. Proportion of responders (with 20% or greater reduction)	The proportion of patients achieving clinical improvement (defined as minimally, much, or very much improved) on the CGI-C at each time point, LOCF.
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Results and Analysis

Analysis description	**Primary Analysis**				
Analysis population and time point description	The Intent-to-Treat (ITT) population was used to assess efficacy. Primary analysis was based on the LOCF dataset using an ANCOVA model (including treatment, center, baseline, and the treatment-by baseline) Time point: 6 weeks of treatment.				
BPRS change from Baseline to endpoint (Day 42/LOCF), ANCOVA, ITT.	Treatment group	Ilo 4-8 md/d	Ilo 10-16 md/d	Ris 4-8 mg/d	Pbo
	Number of subject	153	154	153	156
	Point estimate	Week 6			
	Mean Change	6.7	**7.6**	11.1	2.7
	Adj. Change	6.2	**7.2**	10.3	2.5
	Treatment differences				
		Ilo 4-8 md/d vs. Pbo	**Ilo 10-16 md/d vs. Pbo**	Ris 4-8 mg/d vs. Pbo	
	LS Mean	**3.8**	**4.7**	7.8	
	95% CI	**0.9,6.7**	**1.8,7.5**	4.9,10.7	
	p-value	**0.012**	**0.001**	<0.001	
Note	BPRS mean change was -6.2, -7.2, -10.3, and -2.5 for the ilo 4-8 mg/d, ilo 10-16 mg/d, risperidone, and placebo treatment groups, respectively. There was a statistically significant reduction in the PANSS-derived BPRS score for both iloperidone treatment groups compared to the placebo group at study endpoint.				

Analysis description	**Secondary Analysis**				
(%) Proportion of responders with 20% or greater reduction for PANSS-T, ITT, LOCF	Treatment group	Ilo 4-8 md/d	Ilo 10-16 md/d	Ris 4-8 mg/d	Placebo
	Adj. Change	48	52	61	42
	Treatment differences				
	LS Mean (SE)	6	10	19	
	95% CI	[-5,17]	[-1,21]	[8,30]	
	p-value	0.295	0.164	0.002*	
PANSS-T change from Baseline to endpoint ANCOVA, ITT, LOCF	Adj. Change	9.5	11.1	16.6	3.5
	Treatment differences				
	LS Mean (SE)	6.0	7.6	13.1	
	95% CI	[1.1,10.8]	[2.8,12.3]	[8.3,17.9]	
	p-value	0.017*	0.002*	<0.001*	

	Adj. Change				
	Treatment differences				
	LS Mean (SE)				
	95% CI				
	p-value				
PANSS-P change from Baseline to endpoint (Day 42/LOCF), ANCOVA, ITT, LOCF	Adj. Change	3.5	4.1	6.0	1.6
	Treatment differences				
	LS Mean (SE)	1.9	2.5	4.3	
	95% CI	[0.3,3.4]	[0.9,4.0]	[2.8,5.9]	
	p-value	0.020*	0.002*	<0.001*	
PANSS-N change from Baseline to endpoint (Day 42/LOCF), ANCOVA, ITT, LOCF	Adj. Change	1.9	2.4	3.0	1.0
	Treatment differences				
	LS Mean (SE)	1.9	2.5	4.3	
	95% CI	[0.3,3.4]	[0.9,4.0]	[2.8,5.9]	
	p-value	0.133	0.021*	0.001*	
CGI-S change from baseline, (Day 42/LOCF), ANCOVA, ITT, LOCF	Adj. Change	0.6	0.5	0.8	0.2
	Treatment differences				
	LS Mean (SE)	0.4	0.3	0.6	
	95% CI	[0.1,0.6]	[0.1,0.6]	[0.4,0.9]	
	p-value	0.003*	0.006*	<0.001*	
(%) Proportion of patients achieving a score of "improved", "much improved" or "very much improved" on the CGI-C (Day 42/LOCF), ANCOVA, ITT, LOCF	Adj. Change	54	58	67	43
	Treatment differences				
	LS Mean (SE)	10	15	24	
	95% CI	[-1,22]	[4,26]	[13,35]	
	p-value	0.014*	0.012*	<0.001*	
Note					
Notes	--Regarding the proportion of patients with 20% or greater improvement, significant differences from placebo in the proportion of patients who improved, were not observed for either of the iloperidone groups. -On the PANSS-P score, there were statistically significantly greater reductions in both iloperidone 10-16 mg/d group and iloperidone 4-8 mg/d groups, compared to placebo. -On the PANSS-N score, there were statistically significantly greater reductions in the iloperidone 10-16 mg/d group, but not for iloperidone 4-8 mg/d group (at week 6). -On the CGI-C score, there were statistically significantly greater reductions in both iloperidone 10-16 mg/d group and iloperidone 4-8 mg/d groups, compared to placebo. -On the CGI-C score, there were statistically significantly greater reductions at Weeks 6 in both iloperidone 10-16 mg/d group and iloperidone 4-8 mg/d groups, compared to placebo.				

Table 9 - Summary of efficacy for trial 2301

Title: A multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate prevention of relapse in patients with schizophrenia receiving either flexible dose iloperidone or placebo in long-term use (up to 26 weeks) followed by up to 52 weeks of openlabel extension.	
Study identifier	CILO522D2301

Design	Multicentre, randomized, double-blind, placebo-controlled, parallel group trial including an Iloperidone run-in period (15 to 25 weeks) followed by a randomized, double-blind, placebo-controlled, 26-week relapse prevention phase and optional open-label extension treatment with iloperidone.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Double blind placebo controlled relapse prevention phase (DBRP): 26 weeks -Screening phase: 2 to 4 weeks -Open-label Titration phase: 7 days - Open-label Stabilization phase: 14 to 24 weeks -An optional open-label extension for up to an additional 52 weeks. -An optional additional open-label extension with indefinite duration was available to patients in India and Ukraine
Hypothesis	Superiority of the iloperidone (dosed from 8 to 24 mg/d) group compared to placebo regarding time to relapse or impending relapse based on the log rank test in which the hazard functions of placebo and iloperidone were compared in a relative manner.		
Treatments groups	iloperidone flexible dosing of 8, 12, 16, 20, or 24 mg/day total daily dose given as a bid regimen		Oral capsule. 26 weeks, 97 randomized patients in the DBRP at the interim analysis (for the full final analysis, 151 randomized patients in the iloperidone treatment group)
	Placebo		Oral capsule. 26 weeks, 96 randomized patients (for the final analysis, 150 randomized patients in the iloperidone treatment group)
Endpoints and definitions	Primary endpoint (FAS)	Time to relapse or impending relapse (interim analysis)	Time to relapse or impending relapse defined as the time from the first dose of double-blind study drug to the assessment at which the first time relapse or impending relapse was identified: Hospitalization due to w
	Subsequent primary endpoint (FAS)	Time to event analysis	Time to event analysis
	Subsequent primary endpoint (FAS)	Time to relapse or impending relapse (final analysis)	Idem as the primary analysis except that the analysis will be performed on the final analysis instead of the interim analysis
	Secondary endpoints (LOCF, OC, FAS)	PANSS-T	change from DBRP Baseline at Visit 22a (Visit 22a: Week 26, relapse, or Early Termination) in the PANSS-T score
		CGI-I	change from DBRP Baseline at Visit 22a (Visit 22a: Week 26, relapse, or Early Termination) in the CGI-I scale Percentage of patients with a global improvement rating of no change or improvement (≤4) at endpoint
Database lock	-		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Results from the DBRP of the interim analysis (after 68 events) are considered as the primary results. The efficacy analyses were based on the FAS population Time point: Visit 22a: Week 26, relapse, or Early Termination.		
	Treatment group	**Ilo 8 to 24 mg/d**	PBO

<table>
<tr><td rowspan="5">Primary analysis (Relapse population at the interim analysis)</td><td>Number of analysed patients in the DBRP</td><td>97</td><td>96</td></tr>
<tr><td>Average Time to Relapse</td><td>139</td><td>71</td></tr>
<tr><td>(%) Number of patients relapsed, (95% CI)</td><td>20.4 (12.9, 31.4)</td><td>63.4 (52.7, 74.1)</td></tr>
<tr><td>Number of patients censored (%)</td><td>23</td><td>12</td></tr>
<tr><td>HR (95% CI)</td><td colspan="2">4.7 [2.7, 8.3]</td></tr>
<tr><td>Notes</td><td colspan="3">The interim analysis of the primary efficacy endpoint demonstrated that iloperidone was statistically significantly superior to placebo in preventing relapse or impending relapse. Specifically, the survival curve in the iloperidone group was statistically significantly different from the survival curve in the placebo group (log rank test, p<0.0001).

the estimated hazard ratio and corresponding 95% confidence interval from the Cox regression was 4.7 [2.7, 8.3] indicating that the risk of having a relapse or impending relapse is statistically significantly greater for placebo relative to iloperidone.
In terms of the number of relapse or impending relapse events, there were more events in the placebo group relative to the iloperidone group. The Kaplan-Meier plot at the interim analysis shows that when taking into consideration this time-to-event endpoint, a longer time to relapse or impending relapse in the iloperidone treatment group (relapse rate, 20.4%; average time to relapse, 139 days) is seen compared with the placebo treatment group (relapse rate, 63.4%; average time to relapse, 71 days).</td></tr>
<tr><td>Analysis description</td><td colspan="3">Secondary analysis / Other</td></tr>
<tr><td rowspan="6">Effect estimate per comparison
(only results of the interim analysis are discussed)</td><td>Endpoints</td><td>Ilo 8 to 24 mg/d</td><td>PBO</td></tr>
<tr><td rowspan="2">PANSS-T
(LOCF, FAS)</td><td>2.8</td><td>13.1</td></tr>
<tr><td colspan="2">p<0.0001</td></tr>
<tr><td rowspan="2">CGI-I, adjusted mean change
(LOCF, FAS)</td><td>3.3</td><td>4.4</td></tr>
<tr><td colspan="2">p<0.0001</td></tr>
<tr><td rowspan="2">CGI-I, % of global improvement
(LOCF, FAS)</td><td>83.3</td><td>41.3</td></tr>
<tr><td colspan="2">p<0.0001</td></tr>
<tr><td>Notes</td><td colspan="3">Mean change from randomization baseline at endpoint (Visit 22a) for PANSS-T:
Interim analysis: Patients in the Interim Analysis Population had an average baseline PANSS total score of 76.9 when enrolled into titration/stabilization phase of the study and 57.5 when randomized into the double-blind relapse prevention phase, representing -19.4 points of improvement in overall schizophrenia symptoms. The adjusted mean change from randomization baseline at endpoint in the PANSS total score for the double-blind relapse prevention phase was +2.8 points for iloperidone-treated patients versus +13.1 points for placebo-treated patients (p<0.0001, LOCF).

Mean change for CGI-I:
Interim analysis: At endpoint, the adjusted mean was significantly lower in the iloperidone treatment group (3.3) compared with the placebo treatment group (4.4; p <0.0001). The percentage of patients with a global improvement rating of no change or improvement (⩽4) at endpoint was significantly higher in the iloperidone treatment group (83.3%) compared with the placebo treatment group (41.3%; p < 0.0001). Conversely, the percentage of patients with an overall rating of worsening (>4) was significantly higher in the placebo group (58.8%) compared with the iloperidone treatment group (16.7%; p<0.0001).</td></tr>
</table>

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

Efficacy from the four Phase 3 studies (viz. studies 3000, 3004, 3005 and 3101; studies 3000 and 3005 are discussed below) were pooled and analysed together. Altogether, efficacy data from 2536 subjects were combined (1361 iloperidone, 583 active control, 592 placebo). Using the LOCF model, the pooled efficacy analyses show consistent statistically significant improvement for Iloperidone at doses greater than 10 mg/d compared to placebo on the PANSS-T, PANSS-P, PANSS-N, PANSS-GP, BPRS and CGI-S scores.

Subgroup analyses were performed on the pooled efficacy data, inter alia by diagnosis (schizoaffective or schizophrenia). For the PANSS-T, frequently used as the primary efficacy parameter in the submitted clinical studies, the pooled results excluding patients with schizoaffective disorder showed highly statistically significant differences for Iloperidone 10-16 mg/d and Iloperidone 20-24 mg/d versus placebo. Numerically, the effect size was higher for Iloperidone 20-24 mg/d than Iloperidone 10-16 mg/d. Numerically, haloperidol 15/d and risperidone 4-8 mg/d showed a higher effect size than Iloperidone 20-24 mg/d. The same pattern was shown for BPRS.

Clinical studies in special populations

No dedicated such clinical studies were performed. As for age groups, the main studies included subjects up to the age of 65 years and some supportive clinical studies included subjects up to the age of 69 years

Supportive studies

Short-term efficacy

Clinical study B202. Title of Study: A study of the efficacy of 4 mg and 8 mg iloperidone (HP873) administered to schizofrenic patients for 42 days.

This was a phase 2, prospective, randomized, double-blind, parallel-group, placebo-controlled, multi-center study conducted in male or female patients with acute or relapsing schizophrenia. Due to slow enrolment, this study was discontinued after 104 patients had been randomized and therefore did not reach its targeted enrolment of 120 patients. The protocol-defined primary endpoint was the mean change from baseline in PANSS-T score at Week 6. Patients were randomised and titrated to maintenance doses of Iloperidone 4 mg/d, Iloperidone 8 mg/d or placebo. The primary endpoint was not met.

Clinical study 3000. Title of Study: A prospective, randomized, double-blind, placebo- and active-controlled, multicenter study to evaluate the efficacy and safety of three fixed doses of iloperidone (4, 8, and 12 mg/d) given b.i.d. for 42 days to schizophrenic patients with acute or subacute exacerbation, followed by a doubleblind, active-controlled, flexible-dose, long-term, 20-week phase with iloperidone (4, 8, 12, or 16 mg/d) given q.d..

The design of the study is apparent from the study title and the primary efficacy endpoint was the change from baseline to endpoint (Day 42 or premature discontinuation) on the total score of the PANSS for Iloperidone (average of the 8 mg/d and 12 mg/d dose groups). The active control was haloperidol 15 mg/d. A minimum score of 60 was required on the PANSS-T at baseline. The patient population included subjects with schizoaffective disorder and the proportion of such subjects ranged between 26% and 37% across the treatment groups. The primary endpoint, i.e. the PANSS-T score at Week 6 for Iloperidone (average of the 8 mg/d and 12 mg/d dose groups) compared to placebo, was not met. The primary outcome measurement was statistically significant for the Iloperidone 12 mg/d treatment group, though

without considering multiplicity in the statistical testing. However, the efficacy results for the haloperidol treatment group were more robust and numerically superior to Iloperidone 12 mg/d.

Clinical study 3005 Initial double-blind phase (Days 1-42). Title of Study: A randomized, double-blind, placebo- and risperidonecontrolled, multicenter study to evaluate the efficacy and safety of two non-overlapping dose ranges of iloperidone given bid for 42 days to schizophrenic patients followed by long-term treatment phase with iloperidone given qd

This study was a prospective, randomized, double-blind, placebo- and active-controlled study in patients with acute or subacute exacerbation of schizophrenia. The patient population included subjects with schizoaffective disorders. Patients were randomised to be titrated to four treatment groups: maintenance doses of Iloperidone 12 or 16 mg/d, Iloperidone 20 or 24 mg/d, risperidone 6 or 8 mg/d, or placebo. The study treatment was to be administered b.i.d. Patients were hospitalised for the 3-day placebo run-in period and until the end of the titration period (Day 7), after which they were allowed to take study medication on an outpatient basis. After completing the 6 week initial double-blind phase, patients had the option to continue treatment in the long-term open-label phase of the study (to 1 year). The primary efficacy variable was the change from baseline to endpoint (Day 42 or premature discontinuation) on the 18-item PANSS-derived BPRS using a LOCF dataset in subjects who were randomised, received at least one dose of IMP treatment and had at least one efficacy measurement. The primary treatment comparison was between the Iloperidone 12/16 mg/d group versus placebo. If this treatment comparison showed a statistically significant difference in favour of Iloperidone, Iloperidone treatment 20/24 mg/d would also be compared with placebo. From Week 3 through Week 5 for the ILO 12-16 mg/d group, the adjusted mean change from baseline was statistically superior to placebo. Statistically significant improvement was lost at Week 6, the protocol specified endpoint. Statistically significant results were seen for the Iloperidone group 20/24 mg/d group as of Week 3 throughout Week 6. The efficacy results for the risperidone treatment group were more robust with fewer discontinued patients and numerically superior to the Iloperidone treatment groups. Further, risperidone had a faster onset of action.

Clinical studies 3001, 3002 and 3003. Titles of studies were the same for each study: A prospective, randomized, multi-center, double-blind, flexible-dose, parallel-group study to determine the antipsychotic effect of iloperidone (dose range of 4-16 mg/day, given bid) as compared with haloperidol (dose range 5-20 mg/day, given bid) and to determine the safety of iloperidone in schizophrenic patients

The Applicant has chosen to present these three studies as supportive studies in a joint format in the Clinical Summary of Efficacy since they had identical objectives and designs. The three studies were conducted by Novartis in Europe and Israel (3001), Asia (3002), or South America (3003) to compare maintenance of the antipsychotic effect of Iloperidone compared to haloperidol. The efficacy objective of Studies 3001, 3002, and 3003 was to compare the antipsychotic effect of Iloperidone (4-16 mg /day) with that of haloperidol (5-20 mg /day) in patients with schizophrenia or schizoaffective disorder over 6 weeks and 52 weeks of treatment. The randomisation was uneven and there was no placebo control. A placebo run-in phase lasted 3 days (Day -2 to 0). The initial 6-week double-blind phase consisted of a fixed dose-titration period (Day 1 to 6), a dose adjustment period (Day 7 to 28), and a short-term maintenance period (Day 29 to 42). This was followed by the long-term double-blind phase (Day 43 to 364). The scope here is the efficacy results at Day 42. The efficacy results at Day 364 are presented separately.

The efficacy analysis was based on the intent-to-treat (ITT) population. The ITT population contained all randomized patients who received at least one dose of double-blind study medication and from whom at least one post-baseline efficacy (complete PANSS) measurement was obtained. The primary endpoint was PANSS-T and mean changes from baseline were comparable for the treatments with Iloperidone and

haloperidol. The statistical objectives with the studies were not to show superiority nor non-inferiority for Iloperidone over haloperidol.

Clinical study ILO522DUS01. Title of Study: A 12-week, randomized, multicenter, open-label, iloperidone (12-24 mg/day), flexible dose study assessing efficacy, safety and tolerability of two switch approaches in schizophrenia patients currently receiving Risperidone, Olanzapine, or Aripiprazole (i-FANS)

Study ILO522DUS01 was a 12-week, randomized, multicenter, open-label, flexible dose study assessing the efficacy, safety, and tolerability of two switch approaches in schizophrenia patients currently receiving risperidone, olanzapine, or aripiprazole. Patients were randomized in a 1:1 ratio to either a gradual or immediate switch group within each cohort of prior treatment with risperidone, olanzapine, or aripiprazole. Patients in the immediate switch group discontinued their antipsychotic treatment at the baseline visit while patients in the gradual switch group reduced their antipsychotic treatment to 50% of the original dose. Both groups took their first dose of Iloperidone on the following day. After the first week, patients in the gradual switch group continued on Iloperidone while further reducing their prior treatment to 25% of the original dose for another week, after which they discontinued the medication for the remainder of the study. The primary efficacy endpoint for the study was measured by the Integrated Clinical Global Impression of Change (I-CGI-C) scale at Week 12. There were no statistically significant differences for the primary efficacy endpoint in mean scores observed between the gradual switch group and immediate switch group. The study did not contain any placebo control, nor was any formal non-inferiority analysis planned or conducted between the immediate and gradual switch treatment groups.

Long-term efficacy

Clinical studies 3001, 3002 and 3003. Titles of studies were the same for each study: A prospective, randomized, multi-center, double-blind, flexible-dose, parallel-group study to determine the antipsychotic effect of iloperidone (dose range of 4-16 mg/day, given bid) as compared with haloperidol (dose range 5-20 mg/day, given bid) and to determine the safety of iloperidone in schizophrenic patients

Reference is made to the supportive studies earlier described where the short-term efficacy was described for these studies that also addressed long-term efficacy. Studies 3001, 3002 and 3003 were as mentioned identical (prospective, randomized, multicenter, double blind, flexible-dose, parallel group) studies designed to evaluate the long-term safety and efficacy of iloperidone given at dosages of 4-16 mg per day as compared to haloperidol given at dosages of 5-20 mg per day. The study protocols were amended to include a survival efficacy analysis of the combined data from the three studies mentioned. The amendments were completed and released prior to study completion and database lock.

For the combined analysis of efficacy, the objective was to compare the two treatments in the prevention of relapse during the long-term phase of the study. The efficacy variable of interest was time to relapse. The analysis of comparing time to relapse was based on the survival analysis of time to first relapse. This survival analysis was conducted using a proportional hazards model with time to first relapse as the response variable, and with baseline PANSS total score and treatment group as the independent variables. A two-sided 95% confidence interval was calculated for the hazard ratio of treatment based on this model. A difference between treatments of no greater than 15% in the proportion of patients having a relapse was not considered clinically important. Assuming an expected relapse rate of RH = 30% during the long-term phase of the study for the haloperidol group to demonstrate non-inferiority, the pooled analysis needed to show that iloperidone has a relapse rate RI no greater than RH+15% = 45%. This translates to a hazard ratio between iloperidone and haloperidol of no greater than log (1-RI)/log(1-RH) = 1.676. Iloperidone would thus be considered non-inferior to haloperidol if the upper bound of the

confidence interval for the hazard ratio is 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. There was no placebo control for the purpose of assay sensitivity.

For subjects who had shown improvement or stability at the end of the initial double-blind short term treatment phase (Week 6), the mean time to relapse was 89.8 days for the iloperidone group and 101.8 days for the haloperidol group. The difference between treatment groups was not statistically significant (log rank test; P = 0.8411; Wilcoxon test, P = 0.7637). The analysis of time to relapse based on the proportional hazards model resulted in a hazard ratio of 1.030. Since the upper bound of the calculated confidence interval of the hazard ratio was 1.428 (below 1.676), it was concluded that iloperidone was non-inferior to haloperidol and demonstrates a long-term maintenance of effect.

2.5.2. Discussion on clinical efficacy

Design and conduct of clinical studies

Confirmatory clinical efficacy data for short-term treatment was derived from Study 3101 and - for long-term efficacy - Study 2301 provided confirmatory efficacy data. Study 3004 was previously also considered confirmatory but this study included patients with schizoaffective disorder, and analyses presented for the schizophrenia subgroup did not reach statistical significance. Study 3005 cannot be regarded as confirmatory since it was a negative study and the study population was a mixture of patients with schizophrenia and schizoaffective disorder.

The main short-term (4-week) efficacy study 3101 was appropriately designed and used an appropriate study population although the choice of MMRM for balancing missing values is not regarded as sufficiently rigorous. However, the analysis also included a LOCF imputation for missing efficacy values in subjects who were randomised and had at least one efficacy measurement. The study included an active comparator ziprasidone 160 mg/d. Both Iloperidone and the active comparator were intended to be administered in daily doses at the maximum level (proposed posology for Iloperidone and approved posology for ziprasidone). The endpoints were appropriate, but the original responder definition (≥20% improvement) was questioned, and the Applicant has subsequently presented results from analyses with a revised responder definition (≥30% improvement). Statistical significant differences were not obtained in the responder analyses neither for Iloperidone vs placebo nor for ziprasidone vs placebo.

Several supportive clinical studies were submitted and/or assessed as supportive in this report. The decision to assess these studies as supportive, even if they were submitted as pivotal, was based on a combination of the following factors: the chosen study population (patients with schizoaffective disorder were also included), an inconclusive comparison (no placebo control or no superiority/non-inferiority testing versus active comparator) and/or that the primary endpoint in the primary analysis was not met.

Thus, the following supportive studies addressing short-term efficacy also included subjects with schizoaffective disorder: studies nos. 3000, 3001, 3002, 3003, 3004, and 3005. The following studies were lacking placebo control or superiority/non-inferiority objectives versus active comparator: study ILO522DUS01 and short-term efficacy parts of the identical studies nos. 3001, 3002 and 3003. The long-term efficacy results of pooled results from the identical studies nos. 3001, 3002 and 3003 with time to relapse as primary endpoint, submitted by the Applicant as supportive studies, did besides including subjects with schizoaffective disorder also lack a placebo control to demonstrate assay sensitivity. Instead of the latter, a post hoc historical comparison was used for the purpose of demonstrating assay sensitivity. Such a post hoc historical control can only at best be indicative of assay sensitivity. Furthermore, the non-inferiority testing was not reported on a per-protocol analysis data set, which is an

important analysis population for a non-inferiority testing to investigate whether the used modified intention-to-treat analysis is unduly influenced by poor adherence to study medicine or protocol. The study B202 (short-term efficacy), submitted as a pivotal study, had an appropriate design and study population (i.e. no subjects with schizoaffective disorder) but the primary endpoint was not met. Similarly, the short-term efficacy studies 3000 and 3005 did not meet the primary endpoint for the Iloperidone dose group identified for the primary analysis, but was successful on other Iloperidone dose groups (see below).

Study 2301 (Part A) was a relapse-prevention study used a design where an open label stabilisation phase served to enrich the population for a Double-Blind Relapse Prevention phase. This is appropriate to inform long-term efficacy in patients stabilised under Iloperidone.

The open-label study ILO522DUS01(iFans) compares two ways of switching from other antipsychotics to Iloperidone. Given the absence of patients randomized to receive placebo or a different antipsychotic, this can only be used to conclude on the relative benefits and risks of the two switching approaches.

The Applicant has not addressed the lack of scales informative of social/occupational functioning; the functional improvement of patients has not been studied or shown in any of the main studies. The CGI scale is a rather global assessment and is not specifically informative for patients' social or occupational functioning. The Sheehan disability scale (SDS) is a brief self-report toll and is not optimal to evaluate functioning either.

No conclusive dose-response study was performed with fixed dose levels prior to the phase 3 trials. This represents a considerable draw-back and is a deviation from the product development guideline and as a consequence, the therapeutic dose range based on efficacy needs instead to be inferred from the different phase 3 clinical studies.

The Applicant has a product-specific PIP waiver for all subsets of the paediatric population for Iloperidone in the treatment of schizophrenia and the proposed PI is for use in adult patients with schizophrenia. It is therefore appropriate that the submitted clinical studies do not encompass subjects under the age of 18 years.

The clinical studies listed as main studies in this report did not enrol subjects with an age above 65 years, some supportive clinical studies enrolled subjects with an age up to 69 years. From an efficacy point of view, this is less of an issue but needs to be taken into account with respect to dose recommendations and safety and the overall B/R assessment for the elderly population with schizophrenia.

Efficacy data and additional analyses

For the main study (4-week) 3101, intended to demonstrate short-term efficacy with a fixed daily dose of iloperidone 24 mg/d, the primary endpoint was met in the pre-defined MMRM analysis, but more importantly also with a LOCF imputation technique on subjects who were randomised and had at least one efficacy measurement. In responder analyses, statistical significant differences were not obtained neither for Iloperidone vs placebo nor for ziprasidone vs placebo. Most secondary efficacy endpoints were met in the LOCF analysis. No large numerical efficacy differences were seen between Iloperidone and ziprasidone (160 mg/d), nor in terms of robustness in the results. It is noted that the onset of action appeared to occur later with Iloperidone than with ziprasidone even though both compounds were similarly uptitrated. Thus, in the MMRM and multiple imputation analyses subsequently provided, the effect of ziprasidone in Study 3101 reached statistical significance at Week 2, whereas the effect of Iloperidone (uptitrated in the same way as ziprasidone) reached statistical significance at Week 3 or - in the multiple imputation analyses - Week 4. Several approaches to various data sets support the notion that full efficacy of Iloperidone is not attained before Week 3. For instance, in Study 3101 where full effect

vs placebo would correspond to a reduction of 5 PANSS-T points, it is remarkable that the difference at Week 1 was already 2.4 for ziprasidone, whereas it was 0.1 for Iloperidone. Similarly, at Week 2 it was 4.2 for ziprasidone i.e. almost full efficacy, whereas the difference was still only 2.8 for Iloperidone.

As for the supportive short-term clinical efficacy studies, the prematurely discontinued study B202 in subjects with schizophrenia (exclusively) did not meet the primary endpoint (mean change from baseline on PANSS-T at week 6) for any of the two Iloperidone dosing groups (4 mg/d and 8 mg/d, respectively). The short-term part of study 3000 included also schizoaffective patients and compared Iloperidone in fixed doses of 4 mg/d, 8 mg/d and 12 mg/d with placebo. A fixed dose of haloperidol 15 mg/d was also used. The primary endpoint, i.e. the PANSS-T score at Week 6 for Iloperidone (average of the 8 mg/d and 12 mg/d dose groups) compared to placebo in the LOCF dataset, was not met. The primary outcome measurement was statistically significant for the Iloperidone 12 mg/d treatment group, though without considering multiplicity in the statistical testing. However, the efficacy results for the haloperidol treatment group were more robust and numerically superior to Iloperidone 12 mg/d. Furthermore, in an MMRM analysis of the schizophrenia subpopulation subsequently provided, the effect of haloperidol was statistically significant whereas that of Iloperidone was not. In the two short-term (6-week) efficacy studies 3004 and 3005 with risperidone as comparator both patients with schizophrenia and patients with schizoaffective disorder were enrolled. In Study 3004, the efficacy size for the primary endpoint BPRS mean change from baseline (LOCF analysis) was statistically significant versus placebo, and favoured as for a number of met secondary endpoints numerically the Iloperidone 10-16 mg/d group over the Iloperidone 4-8 mg/d group. Similarly, efficacy size and number of met secondary endpoints favoured numerically risperidone over the two Iloperidone groups. Furthermore, risperidone had a faster onset of action compared to Iloperidone. A significant issue with this study is that post-hoc subgroup analyses in subjects with schizophrenia did not demonstrate a statistically significant result on the primary endpoint. Study 3005 also included patients with schizoaffective disorder and compared two flexible dose levels of Iloperidone (12 or 16 mg/d and 20 or 24 mg/d) with placebo. An active comparator was also used, risperidone in flexible doses of 6 or 8 mg. The primary endpoint in the primary analysis was mean change in BPRS score from baseline to Day 42 for the Iloperidone 12/16 mg/d group and this endpoint was not met. However, based on the results for the primary outcome measurement and the secondary endpoints, efficacy may be claimed for the dose group 20/24 mg/d with caveats for the multiplicity in the testing. The efficacy results for the risperidone treatment group were more robust with fewer discontinued patients and numerically superior to the Iloperidone treatment groups. The short-term efficacy parts of studies 3001, 3002 and 3003 included patients with schizoaffective disorder and used haloperidol as an active comparator, but since no placebo control nor any superiority/non-inferiority testing was planned these studies are inconclusive.

The pooled results from the supportive long-term parts of studies 3001, 3002 and 3003 – and as mentioned subjects with schizoaffective disorder were included in these trial – compared flexible dosing of iloperidone 4-16 mg/d with haloperidol 5-20 mg/d. Non-inferiority was demonstrated for the primary endpoint time to relapse, but with caveats for the methodological limitations earlier discussed.

The daily doses of Iloperidone employed in the clinical studies assessed ranged from 4 mg to 24 mg daily (administered b.i.d.). The Applicant argues that 12 mg/day is an effective dose, since doses as low as 4-8 mg/day were effective in one study (3004), and since in some studies doses of 12 mg/day (3000), 10-16 mg/day (3004) or 12-16 mg/day (3005) likewise showed superiority to placebo. In fact, studies 3000 and 3005 were negative studies, and no correction for multiplicity was performed when evaluating 'superiority' of individual doses. Thus, efficacy has not been convincingly established for 12 mg/day. The Applicant further argues that PK-PD analyses demonstrated a maximum response at exposures of approximately 4 ng/ml, and that a dose of 6 mg bid achieved a mean concentration in excess of this. However, the analysis is fundamentally flawed in that placebo patients were included with an assigned value of zero. If the placebo patients are disregarded in the analysis, there is no meaningful

concentration-response relationship. In conclusion, here is no robust support for any statements concerning dose-response relationship below 24 mg/day (the dose used in study 3101).

An active comparator was included in studies 3000 (Haloperidol), 3004 and 3005 (Risperidone), and 3101 (Ziprasidone). Although comparative efficacy was not the primary objective of those studies, the magnitude of effect of Fanaptum appeared similar to ziprasidone but compared negatively with haloperidol and risperidone.

In the head-to-head short-term clinical efficacy studies Iloperidone showed numerically a smaller effect size and less robustness in the efficacy results than haloperidol 15/mg and risperidone. In the MMRM analysis of Study 3004 (BPRS) presented subsequently the effect of risperidone was highly statistically significant at all timepoints in the schizophrenia subpopulation whereas the effect of Iloperidone did not at any point in time reach statistical significance. As for haloperidol, in Study 3000, the point estimate of the change from baseline for Iloperidone appeared inferior to the one for haloperidol (PANSS-T 5 vs 9 points; BPRS 3 vs. 5 points). No large numerical difference was noted between Iloperidone 24 mg/d and ziprasidone 160 mg/d, which is the maximum daily dose of ziprasidone according to the PI. A consistent finding was the slower onset of action of Iloperidone compared to the other antipsychotics included in the trials even if titration schedules were similar.

The apparent numerically smaller effect size and doubts on the robustness in the efficacy results compared to haloperidol and risperidone are supported by results on the proportion of responders with the threshold of at least ≥30% improvement. Indeed, no statistical differences were demonstrated in each of the short term studies compared to placebo, except for the risperidone Study 3005. Although statistically reached, the proportion of responders (≥30% improvement) was numerically lower for the Iloperidone group compared to risperidone group.

Overall, across all trials, there was a high proportion of patients who prematurely discontinued, and it is not clear that the MMRM, LOCF or OC approaches to handling missing data (as used in the different trials) handle this issue in a sufficiently conservative manner. Analyses of trials 3101, 3004, 3005 and 3000 using baseline observation carried forward (BOCF) have subsequently been presented. In the BOCF-analysis of Study 3101, ziprasidone had a statistically significant effect (2.7 points, p=0.029) on the PANSS-T already at Week 1 whereas the effect of Iloperidone never reached statistical significance. Likewise, in the analysis of the schizophrenia subgroup in Study 3004, the effect of risperidone was statistically significant whereas the effect of Iloperidone never reached statistical significance.

The relatively smaller efficacy of Iloperidone as compared to Risperidone in Studies 3004 and 3005 has been explained by the Applicant to be due to early dropouts. However, drop-outs are not merely a methodological artefact, and the way they are taken into account ultimately shapes the question the study answers. It is well known that the pattern and extent of missing data can itself provide important information for the interpretation of a trial. In particular, the approach suggested by the Applicant does not reflect the overall efficacy of the product and, in absence of baseline predictors of compliance, it seems more natural that any primary Estimand for the trial includes all patients who are randomised to treatment and manage to take it.

The long-term main efficacy study D2301 compared Iloperidone in flexible dosing (8-24 mg/d) with placebo in preventing relapse or impending relapse in long-term use up to 26 weeks. The primary efficacy endpoint (time to event) and most of the secondary efficacy endpoints were met. Iloperidone daily doses of 12 and 16 mg were the most modal doses used. Data drawn from the analysis suggested that drug withdrawal in the placebo group caused a higher relapse rate due possibly to a weaning effect in this group of patients. The Applicant subsequently presented separate analyses on the primary endpoint (time to relapse event) for patients exposed for more than 5 weeks. These analyses confirmed the effect of Iloperidone on time to relapse as compared to placebo in patients who achieved stabilisation with

Iloperidone. As noted by the ad hoc experts group, this does not necessarily imply that Fanaptum would have the same level of efficacy in a population who achieved stabilisation with another treatment. In support to the notion that Iloperidone is also effective and safe in this population, the Applicant claims that the open-label study ILO522DUS01(iFans) suggests that switch to Iloperidone from other antipsychotics is 'tolerated well' whether the switch is immediate or gradual (over 2 weeks). However, an estimation of efficacy cannot be made from an open-label study designed to compare two switching strategies. In addition, 30% of the patients in the study dropped out over the 12-week study period. In the immediate switch group 15% of the patients discontinued permanently due to adverse events vs. 10.4% in the gradual switch group. A total of 18 patients in the immediate switch group and 14 in the gradual switch group had increases in QTcF intervals from baseline to Week 1 that were >30 msec. Orthostatic hypotension was reported as an AE for 13 patients: 4 in the gradual switch group and 9 in the immediate switch group. In conclusion, this open-label study does not necessarily provide evidence that a switch to Iloperidone is tolerated well. It only suggests that if a switch is done, there is no clear difference if it is done gradual or immediate.

Additional expert consultation

The CHMP has sought the advice of an expert group on the following issues related to efficacy:

i) Does the expert group´s consider that iloperidone could be used in the treatment of acute exacerbation of schizophrenia?

ii) Does the expert group´s consider that a target population and a treatment setting could be identified in which the use of iloperidone would be of greater value?

The ad-hoc expert group meeting was held on 5 May 2017.

The Company presented their view in writing and at the meeting.

The experts held the view that Iloperidone may not be appropriate for the treatment of acute exacerbation of schizophrenia due to the need for slow titration and the delayed onset of effect.

The experts also expressed the view that Iloperidone might only be of value in chronic, quite stable patients with mild positive symptoms of schizophrenia who need to discontinue their treatment due to debilitating adverse event – in particular EPS symptoms including akathisia. In selecting a patient population other elements of the safety profile of Iloperidone, including metabolic profile and hypotension, would need to be taken into account. Additionally, the treatment setting should include the availability of a cardiologist to support the interpretation of the ECG examinations.

However, the experts questioned the robustness of the evidence in support of the use of Iloperidone in this population. The study that would most closely inform efficacy in such a setting would be the relapse-prevention study 2301 that followed a randomised-withdrawal design. According to the experts, issues have been noted to preclude a positive conclusion on efficacy in the above described population based on this study:

a. the population is selected – in the enrichment phase - through response to Iloperidone itself and not by stabilisation on another antipsychotic and presence of EPS. This does not directly estimate efficacy in patients stabilised under a different antipsychotic, and in this setting a worsening of the symptoms cannot be excluded on the basis of the currently available evidence.

b. at the beginning of the double-blind randomised withdrawal phase (continuation phase), Iloperidone was stopped without any tapering-down period. This does not allow discriminating whether the difference in relapse rate between patients that continued on Iloperidone and patients

that went on placebo – especially early after randomisation – is due to the efficacy of Iloperidone or due to a withdrawal effect in the placebo arm.

2.5.3. Conclusions on the clinical efficacy

The Applicant has provided demonstration of short-term efficacy. However, the effect size is considered modest. In addition, and also due to the slow titration, the onset of action is slow, which limits the potential usefulness in treating acute exacerbations.

Long-term efficacy, and in particular the ability to prevent relapses in patients stabilised on Iloperidone itself has been shown.

Data are not sufficient to conclude on the ability of Iloperidone to control symptoms and prevent relapses in patients stabilised on a different treatment.

2.6. Clinical safety

Patient exposure

A total of 40 clinical studies have been conducted with Iloperidone. The integrated safety database includes 5530 adult patients with schizophrenia in 11 controlled clinical studies of which 4423 patients were exposed to Iloperidone during at least one phase of the studies i.e. 29 Phase 1 and 2 studies have not been integrated.

Four sets of safety tables have been generated for the 11 integrated Phase 2/3 clinical studies as follows:

1. Study Group 1 – Therapeutic studies of patient with any Iloperidone exposure: all patients enrolled into studies in all phases (controlled and uncontrolled) of all 11 studies combined (please note: patients treated with Iloperidone in this group will have a longer exposure time frame than patients treated with active controls or placebo since these were only available during the double-blind phase);

2. Study Group 2 – Therapeutic studies of patients with any double-blind placebo controlled Iloperidone exposure: patients enrolled only in the double-blind phase of one of the 4 placebo-controlled studies combined;

3. Study Group 3 – Therapeutic studies of patient with any double-blind placebo or active-controlled study phase (excluding any exposure during open label extension phase);

4. Study Group 4 – Open-label Iloperidone exposure: patients who received Iloperidone in the open-label extension phase of any of the 11 studies.

Duration of treatment, Study Group 1 (safety population):

Duration of Treatment Time period	Placebo (N=737)	ILO 4-8 mg/d (N=1311)	ILO 10-16 mg/d (N=2384)	ILO 20-24 mg/d (N=845)	ILO Total (N=4540)	HAL 5-20 mg/d (N=546)	RIS 4-8 mg/d (N=311)	ZIP 160 mg/d (N=184)
Mean (±SD), days	36.6 (36.48)	203.3 (287.85)	237.1 (284.49)	109.1 (145.40)	203.5 (269.42)	175 (155.92)	66.1 (87.84)	20.0 (9.16)
Cumulative duration of treatment:								
>1 Week	654 (88.7%)	1075 (82.0%)	2279 (95.6%)	836 (98.9%)	4190 (92.3%)	499 (91.4%)	285 (91.6%)	168 (91.3%)
>2 Weeks	555 (75.3%)	967 (73.8%)	2133 (89.5%)	776 (91.8%)	3876 (85.4%)	460 (84.2%)	251 (80.7%)	111 (60.3%)
>3 Weeks	491 (66.6%)	882 (67.3%)	2023 (84.9%)	675 (80.0%)	3580 (78.9%)	428 (78.4%)	234 (75.2%)	102 (55.4%)
>4 Weeks	340 (46.1%)	827 (63.1%)	1946 (81.6%)	547 (64.7%)	3320 (73.1%)	408 (74.7%)	224 (72.0%)	4 (2.2%)
>5 Weeks	291 (39.5%)	792 (60.4%)	1879 (78.8%)	527 (62.4%)	3198 (70.4%)	394 (72.2%)	214 (68.8%)	0
>6 Weeks	128 (17.4%)	714 (54.5%)	1710 (71.7%)	500 (59.2%)	2924 (64.4%)	345 (63.2%)	96 (30.9%)	0
>3 Months	52 (7.1%)	553 (42.2%)	1205 (50.5%)	269 (31.8%)	2027 (44.7%)	284 (52.0%)	46 (14.8%)	0
>6 Months	19 (2.6%)	419 (32.0%)	878 (36.8%)	120 (14.2%)	1417 (31.2%)	236 (43.2%)	36 (11.6%)	0
>12 Months	0	242 (18.5%)	497 (20.8%)	50 (5.9%)	789 (17.4%)	24 (4.4%)	6 (1.9%)	0

Data Source: ISS Table 3.1.1 and ISS Table 4.1.1

Table includes data from all phases of Studies 2001, 2301(as of DLP), 3000, 3001, 3002, 3003, 3004, 3005, 3101, US01, and period 1 of 2328.

Demographics and baseline characteristics (safety population):

Characteristics	Placebo (N=737)	ILO 4-8 mg/d (N=1311)	ILO 10-16 mg/d (N=2384)	ILO 20-24 mg/d (N=845)	ILO Comb. (N=4540)	HAL 5-20 mg/d (N=546)	RIS 4-8 mg/d (N=311)	ZIP 160 mg/d (N=184)
Sex								
Male	481 (65.3%)	840 (64.1%)	1526 (64.0%)	617 (73.0%)	2983 (65.7%)	347 (63.6%)	214 (68.8%)	138 (75.0%)
Female	256 (34.7%)	471 (35.9%)	858 (36.0%)	228 (27.0%)	1557 (34.3%)	199 (36.4%)	97 (31.2%)	46 (25.0%)
Age (years)								
N	737	1311	2384	845	4540	546	311	184
Mean	39.2	37.7	38.5	40.2	38.6	36.5	38.8	40.1
SD	10.48	11.04	11.00	10.42	10.93	10.73	11.21	9.64
Median	39.0	37.0	38.0	41.0	39.0	36.0	39.0	41.0
Minimum	18	18	17	18	17	18	17	20
Maximum	69	68	69	65	69	67	67	63
Age (age categories)								
< 50 Years	620 (84.1%)	1116 (85.1%)	1946 (81.6%)	678 (80.2%)	3740 (82.4%)	481 (88.1%)	252 (81.0%)	156 (84.8%)
≥ 50 Years	117 (15.9%)	195 (14.9%)	438 (18.4%)	167 (19.8%)	800 (17.6%)	65 (11.9%)	59 (19.0%)	28 (15.2%)
Race								
Asian	59 (8.0%)	185 (14.1%)	390 (16.4%)	66 (7.8%)	641 (14.1%)	119 (21.8%)	3 (1.0%)	13 (7.1%)
Black/African American	250 (33.9%)	279 (21.3%)	541 (22.7%)	352 (41.7%)	1172 (25.8%)	71 (13.0%)	80 (25.7%)	93 (50.5%)
White	383 (52.0%)	740 (56.4%)	1222 (51.3%)	383 (45.3%)	2345 (51.7%)	287 (52.6%)	210 (67.5%)	67 (36.4%)
Other	45 (6.1%)	107 (8.2%)	231 (9.7%)	44 (5.2%)	382 (8.4%)	69 (12.6%)	18 (5.8%)	11 (6.0%)
Age psychosis was diagnosed (years)								
< 18	122 (16.6%)	221 (16.9%)	368 (15.4%)	131 (15.5%)	720 (15.9%)	96 (17.6%)	52 (16.7%)	30 (16.3%)
18-24	305 (41.4%)	528 (40.3%)	983 (41.2%)	336 (39.8%)	1847 (40.7%)	255 (46.7%)	126 (40.5%)	72 (39.1%)
25-44	275 (37.3%)	514 (39.2%)	942 (39.5%)	344 (40.7%)	1800 (39.6%)	184 (33.7%)	122 (39.2%)	78 (42.4%)
45-65	25 (3.4%)	38 (2.9%)	74 (3.1%)	28 (3.3%)	140 (3.1%)	5 (0.9%)	9 (2.9%)	2 (1.1%)
> 65	0	0	0	0	0	1 (0.2%)	0	0
Missing	10 (1.4%)	10 (0.8%)	17 (0.7%)	6 (0.7%)	33 (0.7%)	5 (0.9%)	0	0
Previous hospitalization for psychosis								
Yes	679 (92.1%)	1170 (89.2%)	1816 (76.2%)	648 (76.7%)	3634 (80.0%)	496 (90.8%)	288 (92.6%)	167 (90.8%)
No	54 (7.3%)	139 (10.6%)	560 (23.5%)	195 (23.1%)	894 (19.7%)	50 (9.2%)	23 (7.4%)	13 (7.1%)
Unknown	4 (0.5%)	2 (0.2%)	8 (0.3%)	2 (0.2%)	12 (0.3%)	0	0	4 (2.2%)

Refer to footnotes on last page. (continued)

Characteristics	Placebo (N=587)	ILO 4-8 mg/d (N=1225)	ILO 10-16 mg/d (N=1533)	ILO 20-24 mg/d (N=452)	ILO Comb. (N=3210)	HAL 5-20 mg/d (N=546)	RIS 4-8 mg/d (N=311)	ZIP 160 mg/d (N=184)
Number of previous hospitalizations for psychosis								
1 – 5	338 (49.8%)	649 (55.5%)	1069 (58.9%)	339 (52.3%)	2057 (56.6%)	285 (57.5%)	143 (49.7%)	78 (46.7%)
6 – 10	153 (22.5%)	283 (24.2%)	389 (21.4%)	157 (24.2%)	829 (22.8%)	113 (22.8%)	70 (24.3%)	40 (24.0%)
11 – 15	95 (14.0%)	105 (9.0%)	174 (9.6%)	71 (11.0%)	350 (9.6%)	42 (8.5%)	38 (13.2%)	21 (12.6%)
16 or more	92 (13.5%)	128 (10.9%)	174 (9.6%)	79 (12.2%)	381 (10.5%)	55 (11.1%)	37 (12.8%)	28 (16.8%)
Missing	1 (0.1%)	5 (0.4%)	10 (0.6%)	2 (0.3%)	17 (0.5%)	1 (0.2%)	0	0
DSM-IV classification of schizophrenia								
10 (Disorganized)	26 (3.5%)	85 (6.5%)	122 (5.1%)	23 (2.7%)	230 (5.1%)	47 (8.6%)	16 (5.1%)	3 (1.6%)
20 (Catatonic)	0	13 (1.0%)	14 (0.6%)	0	27 (0.6%)	6 (1.1%)	0	0
30 (Paranoid)	532 (72.2%)	790 (60.3%)	1403 (58.9%)	563 (66.6%)	2756 (60.7%)	326 (59.7%)	188 (60.5%)	149 (81.0%)
60 (Residual)	1 (0.1%)	57 (4.3%)	106 (4.4%)	0	163 (3.6%)	34 (6.2%)	0	1 (0.5%)
90 (Undifferentiated)	58 (7.9%)	159 (12.1%)	215 (9.0%)	63 (7.5%)	437 (9.6%)	64 (11.7%)	38 (12.2%)	22 (12.0%)
70 (Schizoaffective)						69 (12.6%)	69 (22.2%)	9 (4.9%)
Missing	120 (16.3%)	206 (15.7%)	184 (7.7%)	39 (4.6%)	429 (9.4%)	0	0	0

Data Source: ISS Table.1.1.1

Table includes data from all phases of studies 2001, 2301 (DLP 10 Nov 2014), 3000, 3001, 3002, 3003, 3004, 3005, 3101, US01 and period 1 of Study 2328.
Comb=combined; HAL=haloperidol; ILO=iloperidone; RIS=risperidone; ZIP=ziprasidone.
Percentages are based on the total number of patients within treatment/dose group.
Percentages may not add to 100% due to missing data and/or rounding.
DSM-IV classifications were not collected in study US01.

Adverse events

The overall incidence of adverse events in the Iloperidone group was slightly lower compared to the haloperidol and ziprasidone groups. The incidence of serious adverse events was higher in the Iloperidone group than in the ziprasidone group. More patients in the Iloperidone group had an AE (15.2%) that led to a dose reduction or interruption than in the risperidone (10%) and the ziprasidone (3.3%) groups. Further, slightly more deaths occurred in the Iloperidone group.

Safety profile, Study Group 1 (safety population):

Total n (%) of patients with:	Placebo (N=737)	ILO Comb. (N=4540)	HAL (N=546)	RIS (N=311)	ZIP (N=184)
Adverse Events[a]	**495 (67.2%)**	**3718 (81.9%)**	**503 (92.1%)**	**252 (81.0%)**	**160 (87.0%)**
Severe[b]	81 (11.0%)	744 (16.4%)	164 (30.0%)	47 (15.1%)	15 (8.2%)
Drug-related[c]	276 (37.4%)	2484 (54.7%)	386 (70.7%)	155 (49.8%)	140 (76.1%)
Serious AEs[d]	**53 (7.2%)**	**688 (15.2%)**	**88 (16.1%)**	**32 (10.3%)**	**2 (1.1%)**
Drug-related[e]	11 (1.5%)	95 (2.1%)	18 (3.3%)	7 (2.3%)	0
AEs leading to withdrawal[f]	32 (4.3%)	444 (9.8%)	53 (9.7%)	23 (7.4%)	18 (9.8%)
AEs leading to dose reduction/ interruption[g]	28 (3.8%)	691 (15.2%)	112 (20.5%)	31 (10.0%)	6 (3.3%)
Deaths[h,i]	1 (0.17)	10 (0.40)	1 (0.18)	1 (0.32)	0

Data Source: ISS Table 6.1.1[a], ISS Table 7.1.1[b], ISS Table 8.1.1[c], ISS Table 7.5.1[d], ISS Table 7.9.1[e], ISS Table 11.1[f], ISS Table 9.1.1[g], ISS Table 2.1.1[h]

Table includes data from all phases of Studies 2001, 2301 (DLP 10 Nov 2014), 3000, 3001, 3002, 3003, 3004, 3005, 3101, US01 and period 1 of 2328.
AE=adverse event; HAL=haloperidol; ILO Comb=combined iloperidone; RIS=risperidone; ZIP=ziprasidone
All adverse events are treatment emergent (TEAE).
[i] Includes only deaths that occurred in the 11 integrated studies.

Adverse Events in 5% or more of patients in any treatment group, Study Group 1 (safety population):

SOC Preferred Term	Placebo (N=587)	ILO 4-8 mg/d (N=1225)	ILO 10-16 mg/d (N=1533)	ILO 20-24 mg/d (N=452)	ILO Comb. (N=3210)	HAL 5-20 mg/d (N=546)	RIS 4-8 mg/d (N=311)	ZIP 160 mg/d (N=184)
Total No of TEAEs	*1582*	*4452*	*7835*	*2735*	*15022*	*2246*	*1038*	*655*
N (%) Pts With TEAE	*495 (67.2%)*	*1067 (81.4%)*	*1952 (81.9%)*	*699 (82.7%)*	*3718 (81.9%)*	*503 (92.1%)*	*252 (81.0%)*	*160 (87.0%)*
Cardiac Disorders	**14 (1.9%)**	**76 (5.8%)**	**135 (5.7%)**	**69 (8.2%)**	**280 (6.2%)**	**16 (2.9%)**	**7 (2.3%)**	**6 (3.3%)**
Tachycardia	4 (0.5%)	38 (2.9%)	52 (2.2%)	47 (5.6%)	137 (3.0%)	10 (1.8%)	3 (1.0%)	3 (1.6%)
Gastrointestinal Disorders	**194 (26.3%)**	**344 (26.2%)**	**613 (25.7%)**	**290 (34.3%)**	**1247 (27.5%)**	**146 (26.7%)**	**116 (37.3%)**	**83 (45.1%)**
Nausea	43 (5.8%)	97 (7.4%)	148 (6.2%)	56 (6.6%)	301 (6.6%)	23 (4.2%)	30 (9.6%)	25 (13.6%)
Dry Mouth	7 (0.9%)	63 (4.8%)	167 (7.0%)	100 (11.8%)	330 (7.3%)	13 (2.4%)	11 (3.5%)	13 (7.1%)
Constipation	51 (6.9%)	59 (4.5%)	83 (3.5%)	54 (6.4%)	196 (4.3%)	34 (6.2%)	18 (5.8%)	16 (8.7%)
Vomiting	34 (4.6%)	64 (4.9%)	88 (3.7%)	28 (3.3%)	180 (4.0%)	18 (3.3%)	28 (9.0%)	15 (8.2%)
Diarrhoea	25 (3.4%)	50 (3.8%)	100 (4.2%)	39 (4.6%)	189 (4.2%)	18 (3.3%)	11 (3.5%)	12 (6.5%)
Dyspepsia	40 (5.4%)	47 (3.6%)	69 (2.9%)	44 (5.2%)	160 (3.5%)	21 (3.8%)	20 (6.4%)	20 (10.9%)
Abdominal discomfort	25 (3.4%)	21 (1.6%)	34 (1.4%)	35 (4.1%)	90 (2.0%)	7 (1.3%)	14 (4.5%)	13 (7.1%)
General Disorders and Administration Site Conditions	**65 (8.8%)**	**198 (15.1%)**	**355 (14.9%)**	**128 (15.1%)**	**681 (15.0%)**	**71 (13.0%)**	**36 (11.6%)**	**31 (16.8%)**
Fatigue	20 (2.7%)	70 (5.3%)	128 (5.4%)	51 (6.0%)	249 (5.5%)	28 (5.1%)	5 (1.6%)	15 (8.2%)
Infections and Infestations	**67 (9.1%)**	**249 (19.0%)**	**491 (20.6%)**	**136 (16.1%)**	**876 (19.3%)**	**109 (20.0%)**	**52 (16.7%)**	**19 (10.3%)**
Nasopharyngitis	20 (2.7%)	70 (5.3%)	127 (5.3%)	42 (5.0%)	239 (5.3%)	17 (3.1%)	12 (3.9%)	4 (2.2%)
Investigations	**31 (4.2%)**	**88 (6.7%)**	**234 (9.8%)**	**168 (19.9%)**	**490 (10.8%)**	**16 (2.9%)**	**18 (5.8%)**	**29 (15.8%)**
Weight Increased	9 (1.2%)	37 (2.8%)	112 (4.7%)	94 (11.1%)	243 (5.4%)	5 (0.9%)	10 (3.2%)	8 (4.3%)
Musculoskeletal and Connective Tissue Disorders	**83 (11.3%)**	**180 (13.7%)**	**250 (10.5%)**	**117 (13.8%)**	**547 (12.0%)**	**122 (22.3%)**	**44 (14.1%)**	**32 (17.4%)**
Back Pain	21 (2.8%)	47 (3.6%)	69 (2.9%)	26 (3.1%)	142 (3.1%)	24 (4.4%)	13 (4.2%)	10 (5.4%)

Refer to footnotes on last page. (continued)

SOC Preferred Term	Placebo (N=587)	ILO 4-8 mg/d (N=1225)	ILO 10-16 mg/d (N=1533)	ILO 20-24 mg/d (N=452)	ILO Comb. (N=3210)	HAL 5-20 mg/d (N=546)	RIS 4-8 mg/d (N=311)	ZIP 160 mg/d (N=184)
Nervous System Disorders	**220 (29.9%)**	**543 (41.4%)**	**962 (40.4%)**	**382 (45.2%)**	**1887 (41.6%)**	**370 (67.8%)**	**162 (52.1%)**	**114 (62.0%)**
Headache	122 (16.6%)	221 (16.9%)	326 (13.7%)	138 (16.3%)	685 (15.1%)	77 (14.1%)	71 (22.8%)	39 (21.2%)
Dizziness	45 (6.1%)	169 (12.9%)	303 (12.7%)	135 (16.0%)	607 (13.4%)	29 (5.3%)	26 (8.4%)	24 (13.0%)
Tremor	13 (1.8%)	58 (4.4%)	115 (4.8%)	26 (3.1%)	199 (4.4%)	147 (26.9%)	22 (7.1%)	6 (3.3%)
Somnolence	14 (1.9%)	68 (5.2%)	155 (6.5%)	65 (7.7%)	288 (6.3%)	36 (6.6%)	19 (6.1%)	14 (7.6%)
Akathisia	16 (2.2%)	58 (4.4%)	99 (4.2%)	26 (3.1%)	183 (4.0%)	118 (21.6%)	22 (7.1%)	15 (8.2%)
Sedation	18 (2.4%)	46 (3.5%)	97 (4.1%)	77 (9.1%)	220 (4.8%)	10 (1.8%)	16 (5.1%)	44 (23.9%)
Extrapyramidal Disorder	25 (3.4%)	59 (4.5%)	73 (3.1%)	27 (3.2%)	159 (3.5%)	84 (15.4%)	30 (9.6%)	17 (9.2%)
Dyskinesia	10 (1.4%)	33 (2.5%)	41 (1.7%)	6 (0.7%)	80 (1.8%)	28 (5.1%)	7 (2.3%)	1 (0.5%)
Muscle Rigidity	1 (0.1%)	19 (1.4%)	27 (1.1%)	4 (0.5%)	50 (1.1%)	45 (8.2%)	14 (4.5%)	1 (0.5%)
Bradykinesia	0	15 (1.1%)	24 (1.0%)	3 (0.4%)	42 (0.9%)	31 (5.7%)	5 (1.6%)	0
Dystonia	4 (0.5%)	9 (0.7%)	30 (1.3%)	3 (0.4%)	42 (0.9%)	47 (8.6%)	11 (3.5%)	5 (2.7%)
Psychiatric Disorders	**259 (35.1%)**	**629 (48.0%)**	**1107 (46.4%)**	**233 (27.6%)**	**1969 (43.4%)**	**342 (62.6%)**	**135 (43.4%)**	**50 (27.2%)**
Insomnia	113 (15.3%)	277 (21.1%)	533 (22.4%)	83 (9.8%)	893 (19.7%)	189 (34.6%)	49 (15.8%)	14 (7.6%)
Anxiety	67 (9.1%)	179 (13.7%)	316 (13.3%)	42 (5.0%)	537 (11.8%)	104 (19.0%)	43 (13.8%)	10 (5.4%)
Agitation	90 (12.2%)	168 (12.8%)	223 (9.4%)	33 (3.9%)	424 (9.3%)	80 (16.1%)	37 (11.9%)	12 (6.5%)
Psychotic Disorder	15 (2.0%)	72 (5.5%)	181 (7.6%)	30 (3.6%)	283 (6.2%)	35 (6.4%)	7 (2.3%)	4 (2.2%)
Schizophrenia	39 (5.3%)	74 (5.6%)	146 (6.1%)	35 (4.1%)	255 (5.6%)	18 (3.3%)	12 (3.9%)	1 (0.5%)
Restlessness	25 (3.4%)	51 (3.9%)	120 (5.0%)	30 (3.6%)	201 (4.4%)	74 (13.6%)	24 (7.7%)	10 (5.4%)
Respiratory Disorders	**48 (6.5%)**	**148 (11.3%)**	**276 (11.6%)**	**121 (14.3%)**	**545 (12.0%)**	**38 (7.0%)**	**34 (10.9%)**	**26 (14.1%)**
Nasal Congestion	14 (1.9%)	62 (4.7%)	123 (5.2%)	54 (6.4%)	239 (5.3%)	9 (1.6%)	9 (2.9%)	8 (4.3%)

Data Source: ISS Table 6.1.1

Table includes data from all phases of Studies 2001, 2301 (DLP 10 Nov 2014), 3000, 3001, 3002, 3003, 3004, 3005, 3101, US01 and period 1 of Study 2328.

HAL=haloperidol; ILO Comb=combined iloperidone; RIS=risperidone; TEAE=treatment-emergent adverse event; ZIP=ziprasidone

Patients who experienced multiple AEs within the same SOC were counted only once for that same SOC.

Patients who experienced the same AE multiple times within the same SOC were counted only once for the corresponding Preferred Term.

Adverse events are sorted alphabetically by SOC and within each SOC the preferred term is presented by decreasing order of frequency in the combined iloperidone group.

Percentages are based on the total number of patients within each treatment/dose group.

Severe Adverse Events in ⩾0.5% of patients in any treatment group, Study Group 1 (safety population):

SOC Preferred Term	Placebo (N=737)	ILO 4-8 mg/d (N=1311)	ILO 10-16 mg/d (N=2384)	ILO 20-24 mg/d (N=845)	ILO Comb. (N=4540)	HAL 5-20 mg/d (N=546)	RIS 4-8 mg/d (N=311)	ZIP 160 mg/d (N=184)
Total n with any TEAEs	495 (67.2%)	1067 (81.4%)	1952 (81.9%)	699 (82.7%)	3718 (81.9%)	503 (92.1%)	252 (81.0%)	160 (87.0%)
Total n (%) with severe TEAEs	81 (11.0%)	265 (20.2%)	409 (17.2%)	70 (8.3%)	744 (16.4%)	164 (30.0%)	47 (15.1%)	15 (8.2%)
Total no. of severe TEAEs	89	400	674	101	1175	307	58	21
Eye Disorders	**0**	**1 (0.1%)**	**3 (0.1%)**	**0**	**4 (0.1%)**	**4 (0.7%)**	**1 (0.3%)**	**0**
Oculogyric crisis	0	0	0	0	0	3 (0.5%)	1 (0.3%)	0
Gastrointestinal Disorders	**1 (0.1%)**	**18 (1.4%)**	**26 (1.7%)**	**7 (1.5%)**	**58 (1.3%)**	**5 (0.9%)**	**1 (0.3%)**	**1 (0.5%)**
Nausea	1 (0.1%)	6 (0.5%)	5 (0.2%)	0	11 (0.2%)	1 (0.2%)	0	0
Diarrhoea	0	0	1 (0.0%)	1 (0.1%)	2 (0.0%)	0	0	1 (0.5%)
General Disorders and Administration Site Conditions	**0**	**9 (0.7%)**	**20 (0.8%)**	**2 (0.2%)**	**31 (0.7%)**	**8 (1.5%)**	**1 (0.3%)**	**2 (1.1%)**
Pain	0	1 (0.1%)	0	0	1 (0.0%)	0	0	1 (0.5%)
Chest discomfort	0	0	0	1 (0.1%)	1 (0.0%)	0	0	1 (0.5%)
Investigations	**2 (0.3%)**	**6 (0.5%)**	**12 (0.5%)**	**4 (0.5%)**	**22 (0.5%)**	**4 (0.7%)**	**4 (1.3%)**	**0**
Weight Increased	0	1 (0.1%)	3 (0.1%)	1 (0.1%)	5 (0.1%)	2 (0.4%)	2 (0.6%)	0
Metabolism and Nutrition Disorders	**1 (0.1%)**	**2 (0.2%)**	**11 (0.5%)**	**1 (0.1%)**	**14 (0.3%)**	**0**	**6 (3.3%)**	**1 (0.5%)**
Decreased appetite	0	0	2 (0.1%)	0	2 (0.0%)	0	0	1 (0.5%)
Musculoskeletal and Connective Tissue Disorders	**1 (0.2%)**	**9 (0.7%)**	**9 (0.4%)**	**1 (0.1%)**	**19 (0.4%)**	**12 (2.2%)**	**0**	**2 (1.1%)**
Back Pain	0	2 (0.2%)	0	0	2 (0.0%)	2 (0.4%)	0	2 (1.1%)
Muscle Rigidity	0	1 (0.1%)	0	0	1 (0.0%)	8 (1.5%)	0	0
Nervous System Disorders	**8 (1.1%)**	**32 (2.4%)**	**37 (1.6%)**	**13 (1.5%)**	**82 (1.8%)**	**75 (13.7%)**	**11 (3.5%)**	**6 (3.3%)**
Akathisia	1 (0.1%)	6 (0.5%)	8 (0.3%)	0	14 (0.3%)	22 (4.0%)	0	1 (0.5%)
Headache	2 (0.3%)	7 (0.5%)	6 (0.3%)	4 (0.5%)	17 (0.4%)	1 (0.2%)	1 (0.3%)	5 (2.7%)
Tremor	0	5 (0.4%)	1 (0.1%)	0	6 (0.1%)	30 (5.5%)	1 (0.3%)	0
Dyskinesia	1 (0.1%)	2 (0.2%)	2 (0.1%)	1 (0.1%)	5 (0.1%)	7 (1.3%)	0	0
Dystonia	0	2 (0.2%)	2 (0.1%)	1 (0.1%)	5 (0.1%)	12 (2.2%)	1 (0.3%)	0
Extrapyramidal Disorder	0	1 (0.1%)	2 (0.1%)	0	3 (0.1%)	14 (2.6%)	3 (1.0%)	0
Muscle Rigidity	0	1 (0.1%)	1 (0.0%)	0	2 (0.0%)	13 (2.4%)	1 (0.3%)	0
Drooling	0	1 (0.1%)	0	0	0	3 (0.5%)	0	0
Sedation	0	0	0	2 (0.2%)	2 (0.0%)	0	0	1 (0.5%)
Parkinsonism	0	0	0	0	0	0	0	1 (0.5%)
Bradykinesia	0	0	1 (0.0%)	0	1 (0.0%)	10 (1.8%)	0	0
Psychiatric Disorders	**65 (8.8%)**	**183 (14.0%)**	**295 (12.4%)**	**41 (4.9%)**	**519 (11.4%)**	**97 (17.8%)**	**29 (9.3%)**	**6 (3.3%)**
Psychotic Disorder	9 (1.2%)	38 (2.9%)	41 (3.8%)	7 (0.8%)	142 (3.1%)	18 (3.3%)	4 (1.3%)	1 (0.5%)
Schizophrenia	18 (2.4%)	42 (3.2%)	69 (4.2%)	15 (1.8%)	126 (2.8%)	11 (2.0%)	9 (2.9%)	1 (0.5%)
Agitation	18 (2.4%)	40 (3.1%)	41 (1.7%)	7 (0.8%)	88 (1.9%)	20 (3.7%)	4 (1.3%)	2 (1.1%)
Anxiety	5 (0.7%)	21 (1.6%)	42 (1.8%)	0	63 (1.4%)	18 (3.3%)	6 (1.9%)	2 (1.1%)
Insomnia	4 (0.5%)	16 (1.2%)	28 (1.2%)	2 (0.2%)	46 (1.0%)	13 (2.4%)	2 (0.6%)	0
Delusion	1 (0.1%)	8 (0.6%)	17 (0.7%)	0	25 (0.6%)	2 (0.4%)	1 (0.3%)	0
Suicidal Ideation	3 (0.4%)	8 (0.6%)	11 (0.5%)	3 (0.4%)	22 (0.5%)	5 (0.9%)	2 (0.6%)	0
Depression	2 (0.3%)	7 (0.5%)	11 (0.5%)	2 (0.2%)	20 (0.4%)	3 (0.5%)	0	0
Suicide Attempt	0	7 (0.5%)	8 (0.5%)	1 (0.2%)	17 (0.4%)	2 (0.4%)	1 (0.3%)	0
Aggression	4 (0.5%)	2 (0.2%)	13 (0.8%)	0	15 (0.3%)	2 (0.4%)	1 (0.3%)	0
Hallucination	0	1 (0.1%)	8 (0.3%)	0	9 (0.2%)	1 (0.2%)	0	0
Restlessness	0	2 (0.2%)	7 (0.3%)	0	9 (0.2%)	17 (3.1%)	1 (0.3%)	1 (0.5%)
Hostility	0	0	6 (0.3%)	0	6 (0.1%)	1 (0.2%)	0	0

Data Source: ISS Table 7.1.1
Table includes data from Studies 2001, 2301 (DLP 10 Nov 2014), 3000, 3001, 3002, 3003, 3004, 3005, 3101, US01 and period 1 of 2328.
HAL=haloperidol; ILO Comb=combined iloperidone; RIS=risperidone; ZIP=ziprasidone
Severe adverse events are defined as those deemed by the investigator as being "severe" in nature.
Patients experiencing the same Adverse Event multiple times will only be counted once for the corresponding Preferred Term based on the greatest extent of severity. Similarly, patients experiencing multiple adverse events within the same System Organ Class (SOC) will be counted only once for that same System Organ Class.
Adverse Events are sorted alphabetically by SOC and within each SOC the Preferred Term is presented by decreasing order of total frequency in the Combined Iloperidone Group.
Percentages are based on the total number of patients within treatment/dose group.

Adverse Events by Duration of Treatment

Incidence of Adverse Events by observation time by overall frequency, severity and drug relationship in the placebo and combined iloperidone treatment groups, Study Group 1 (safety population):

	Placebo			ILO Comb.		
Treatment Period	**All AEs**	**Related AEs**	**Severe AEs**	**All AEs**	**Related AEs**	**Severe AEs**
Total number of TEAEs	*1582*	*621*	*89*	*15022*	*6345*	*1175*
N (%) with at least one TEAE	*495 (67.2%)*	*276 (37.4%)*	*81 (11.0%)*	*3718 (81.9%)*	*2484 (54.7%)*	*744 (16.4%)*
N (%) with TEAEs during observation time:						
0-6 wks	477 (64.7%)	266 (36.1%)	79 (10.7%)	3177 (70.0%)	2045 (45.0%)	373 (8.2%)
>6 wks-6 mos	25 (19.5%)	11 (8.6%)	2 (1.6%)	1454 (49.7%)	717 (24.5%)	246 (8.4%)
>6 mos-12 mos	-	-	-	651 (45.9%)	249 (17.6%)	131 (9.2%)
>12 mos	-	-	-	435 (55.1%)	159 (20.2%)	102 (12.9%)

Data Source: ISS Table 10.1.1
Table includes data from all phases of Studies 2001, 2301 (DLP 10 Nov 2014), 3000, 3001, 3002, 3003, 3004, 3005, 3101, US01 and period 1 of Study 2328
AE=adverse event; ILO Comb=combined iloperidone; TEAE=treatment-emergent adverse event
Patients with newly emergent adverse events may be counted in multiple observation times if 1) a TEAE has appeared for the first time, or 2) the TEAE appeared in an earlier observation period but had resolved before reappearing, or if the patient developed a different TEAE for the first time within that observation period.

Analysis of Adverse Events by Organ System or Syndrome

Seizures

There was no dose-related increase in seizures among the 3 Iloperidone dose groups. There was also no duration-related pattern in the occurrence of seizures. Seizures occurred with a similar frequency across treatment groups.

Extrapyramidal Symptoms

Extrapyramidal symptoms (EPS) reported as adverse events occurred less frequently in the Iloperidone group compared to the other active treatment groups but more frequently compared to placebo.

Extrapyramidal Symptoms Safety profile for patients with extrapyramidal symptoms, Study Group 1 (safety population):

Number (%) of patients with:	**Placebo (N=737)**	**ILO Comb. (N=4540)**	**HAL 5-20 mg/d (N=546)**	**RIS 4-8 mg/d (N=311)**	**ZIP 160 mg/d (N=184)**
EPS AE	72 (9.8%)	729 (16.1%)	328 (60.1%)	4 (30.2%)	47 (25.5%)
Severe EPS AE	2 (0.3%)	34 (0.7%)	67 (12.3%)	7 (2.3%)	2 (1.1%)
Drug-related EPS AE	59 (8.0%)	592 (13.0%)	307 (56.2%)	80 (25.7%)	46 (25.0%)
Serious EPS AE	0	10 (0.2%)	11 (2.0%)	4 (1.3%)	0
Tx discontinued for EPS AE	2 (0.3%)	22 (0.5%)	30 (5.5%)	4 (1.3%)	3 (1.6%)
Death due to EPS AE	0	0	0	0	0

Data Source: ISS Table 21.1.1, ISS Table 21.2.1, ISS Table 21.3.1, ISS Table 21.4.1, ISS Table 21.5.1, ISS Table 21.6.1, ISS Table 21.7.1 and ISS Table 21.8.1
Table includes data from all phases of Studies 2001, 2301 (DLP 10 NOV 2014), 3000, 3001, 3002, 3003, 3004, 3005, 3101, US01 and period 1 of Study 2328 (treatment without metabolic inhibitors).
Comb=combined; HAL=haloperidol; ILO=iloperidone; RIS=risperidone; ZIP=ziprasidone

Extrapyramidal Symptoms Rating Scale

The adverse event findings for EPS were corroborated by the results for the Extrapyramidal Symptoms Rating Scale (ESRS). For the combined Iloperidone group in Study Group 1, the mean change from baseline to worst value during treatment in the overall rating score (0.99) was higher than that for the placebo group (0.64), lower than that for haloperidol group (4.00), and similar to that for the 2 other active comparator groups (RIS, 1.57; ZIP, 0.94). There was a slight dose-related increase.

Summary of select parameters in the extrapyramidal symptoms rating scale, Study Group 1 (safety population):

ESRS parameter	Placebo (N=587)	ILO 4-8 mg/d (N=1225)	ILO 10-16 mg/d (N=1533)	ILO 20-24 mg/d (N=452)	ILO Comb. (N=3210)	HAL 5-20 mg/d (N=546)	RIS 4-8 mg/d (N=311)	ZIP 160 mg/d (N=184)
Overall Rating								
Mean baseline score	2.21	2.41	2.52	1.27	2.30	2.59	2.55	1.30
	(3.092)	(3.674)	(3.605)	(2.075)	(3.483)	(3.558)	(3.504)	(1.945)
Worst score during tx,	2.85	3.19	3.64	2.35	3.30	6.59	4.12	2.24
mean (±SD)	(3.465)	(4.017)	(4.237)	(3.379)	(4.067)	(5.725)	(4.079)	(2.844)
Mean (±SD) change	0.64	0.78	1.13	1.09	0.99	4.00	1.57	0.94
from BL to worst score	(2.662)	(3.446)	(3.559)	(2.696)	(3.411)	(5.196)	(3.544)	(2.341)
Dyskinesia								
Mean baseline score	0.26	0.21	0.26	0.16	0.23	0.17	0.39	0.2
	(0.695)	(0.685)	(0.767)	(0.472)	(0.703)	(0.584)	(0.984)	(0.571)
Worst score during tx,	0.41	0.36	0.42	0.3	0.38	0.67	0.54	0.29
mean (±SD)	(0.873)	(0.907)	(0.933)	(0.812)	(0.908)	(1.19)	(1.062)	(0.684)
Mean (±SD) change	0.15	0.15	0.16	0.14	0.16	0.5	0.15	0.09
from BL to worst score	(0.725)	(0.757)	(0.825)	(0.701)	(0.783)	(1.086)	(0.835)	(0.497)
Parkinsonism								
Mean baseline score	1.46	1.66	1.78	0.82	1.60	1.86	1.70	0.75
	(2.348)	(2.704)	(2.739)	(1.537)	(2.609)	(2.752)	(2.466)	(1.343)
Worst score during tx,	1.87	2.31	2.70	1.74	2.42	4.89	2.95	1.45
mean (±SD)	(2.501)	(2.947)	(3.148)	(2.667)	(3.028)	(4.451)	(3.193)	(2.101)
Mean (±SD) change	0.41	0.65	0.92	0.92	0.82	3.03	1.25	0.70
from BL to worst score	(1.963)	(2.708)	(2.789)	(2.228)	(2.689)	(4.060)	(2.731)	(1.891)
Dystonia								
Mean baseline score	0.02	0.05	0.03	0.0	0.04	0.06	0.04	0.03
	(0.126)	(0.283)	(0.236)	(0.048)	(0.239)	(0.273)	(0.237)	(0.164)
Worst score during tx,	0.06	0.06	0.11	0.02	0.08	0.26	0.10	0.05
mean (±SD)	(0.274)	(0.309)	(0.423)	(0.178)	(0.358)	(0.689)	(0.451)	(0.296)
Mean (±SD) change	0.04	0.02	0.08	0.02	0.05	0.21	0.06	0.02
from BL to worst score	(0.239)	(0.327)	(0.416)	(0.172)	(0.36)	(0.694)	(0.496)	(0.299)

ESRS parameter	Placebo (N=587)	ILO 4-8 mg/d (N=1221)	ILO 10-16 mg/d (N=1530)	ILO 20-24 mg/d (N=440)	ILO Comb. (N=3191)	HAL 5-20 mg/d (N=546)	RIS 4-8 mg/d (N=306)	ZIP 160 mg/d (N=150)
Akathisia								
Mean baseline score	0.45	0.47	0.46	0.34	0.45	0.49	0.52	0.51
	(0.92)	(0.94)	(0.93)	(0.82)	(0.92)	(0.97)	(0.99)	(0.96)
Worst score during tx,	0.75	0.67	0.73	0.49	0.67	1.32	0.95	0.91
mean (±SD)	(1.16)	(1.09)	(1.15)	(0.91)	(1.10)	(1.40)	(1.31)	(1.32)
Mean (±SD) change	0.3	0.2	0.27	0.14	0.22	0.83	0.43	0.4
from BL to worst score	(0.90)	(0.91)	(1.02)	(0.74)	(0.94)	(1.26)	(1.20)	(0.95)
Total rigidity								
Mean baseline score	0.78	1.35	1.32	0.50	1.22	1.65	0.89	0.68
	(1.99)	(2.89)	(2.78)	(1.54)	(2.70)	(3.23)	(2.14)	(2.06)
Worst score during tx,	1.07	1.66	1.91	0.84	1.67	4.33	1.78	0.96
mean (±SD)	(2.21)	(3.09)	(3.16)	(2.11)	(3.03)	(4.83)	(2.83)	(2.33)
Mean (±SD) change	0.29	0.30	0.59	0.34	0.45	2.68	0.89	0.27
from BL to worst score	(1.63)	(2.46)	(2.71)	(1.85)	(2.51)	(4.01)	(2.56)	(2.30)
Total tremor								
Mean baseline score	0.76	1.18	1.34	0.81	1.21	1.52	1.21	0.74
	(2.01)	(2.90)	(3.11)	(2.37)	(2.94)	(3.58)	(3.18)	(1.88)
Worst score during tx,	1.14	1.55	2.11	1.15	1.78	4.36	2.09	1.21
mean (±SD)	(2.208)	(2.881)	(3.552)	(2.075)	(3.170)	(6.121)	(3.893)	(2.505)
Mean (±SD) change	0.37	0.36	0.75	0.35	0.55	2.85	0.88	0.48
from BL to worst score	(1.752)	(2.521)	(2.841)	(1.686)	(2.607)	(4.908)	(2.591)	(1.754)

Data Source: ISS Table 18.1.1

Table includes data from all phases of Studies 2001, 2301 (DLP 10 NOV 2014), 3000, 3001, 3002, 3003, 3004, 3005, 3101, US01 and period 1 of Study 2328.

BL=baseline; Comb=combined; HAL=haloperidol; ILO=iloperidone; RIS=risperidone; tx=treatment; ZIP=ziprasidone

Barnes Akathisia Scale

For Study Group 1, approximately three-quarters or more of patients across all treatment groups did not have signs or symptoms of akathisia at baseline according to the Barnes Akathisia Scale (BAS). The percentage of patients whose Objective Assessment of Akathisia Score worsened from baseline was

similar for the placebo (14.4%) and combined Iloperidone (17.2%) groups, and higher for risperidone (27.0%),ziprasidone (24.5%), and the haloperidol (40.7%) group.

Summary of Barnes Akathisia Scale, Study Group 1 (safety population):

BAS parameter	Placebo ((N=610)	ILO 4-8 mg/d (N=1046)	ILO 10-16 mg/d (N=1913)	ILO 20-24 mg/d (N=688)	ILO Comb. (N=3647)	HAL 5-20 mg/d (N=428)	RIS 4-8 mg/d (N=311)	ZIP 160 mg/d (N=184)
Objective Assessment of Akathisia Score								
N evaluated at BL	597	977	1857	614	3448	428	296	147
N (%) normal at BL	469 (78.6%)	776 (79.4%)	1514 (81.5%)	507 (82.6%)	2797 (81.1%)	327 (76.4%)	210 (70.9%)	115 (78.2%)
N evaluated at worst value	597	977	1857	614	3448	428	296	147
Change from baseline to worst value:								
Improved	38 (6.4%)	63 (6.4%)	109 (5.9%)	37 (6.0%)	209 (6.1%)	17 (4.0%)	27 (9.1%)	7 (4.8%)
No Change	473 (79.2%)	725 (74.2%)	1418 (76.4%)	504 (82.1%)	2647 (76.8%)	237 (55.4%)	189 (63.9%)	104 (70.7%)
Worsened	86 (14.4%)	189 (19.3%)	330 (17.8%)	73 (11.9%)	592 (17.2%)	174 (40.7%)	80 (27.0%)	36 (24.5%)
Subjective Awareness of Restlessness								
N evaluated at BL	597	976	1857	615	3448	428	296	147
N (%) Absent at BL	455 (74.5%)	719 (73.7%)	1413 (76.1%)	471 (76.6%)	2603 (75.5%)	306 (71.5%)	196 (64.5%)	100 (68.0%)
N evaluated at worst value	597	976	1857	615	3448	428	296	147
Change from baseline to worst value:								
Improved	46 (7.7%)	80 (8.2%)	142 (7.6%)	55 (8.9%)	277 (8.0%)	17 (4.0%)	30 (10.1%)	9 (6.1%)
No Change	460 (77.1%)	685 (70.2%)	1340(72.2%)	451 (73.3%)	2476 (71.8%)	197 (46.0%)	172 (58.1%)	97 (66.0%)
Worsened	91 (15.2%)	211 (21.6%)	375 (20.2%)	109 (17.7%)	695 (20.2%)	214 (50.0%)	94 (31.8%)	41 (27.9%)
Subjective Distress Related to Restlessness Akathisia Score								
N evaluated at BL	597	976	1857	615	3448	428	296	147
N (%) No Distress at BL	485 (81.2%)	796 (81.6%)	1539 (82.9%)	520 (84.6%)	2855 (82.8%)	337 (78.7%)	220 (74.3%)	124 (84.4%)
N evaluated at worst value	597	976	1857	615	3448	428	296	147
Change from baseline to worst value:								
Improved	41 (6.9%)	67 (6.9%)	117 (6.3%)	32 (5.2%)	216 (6.3%)	14 (3.3%)	23 (7.8%)	8 (5.4%)
No Change	469 (78.6%)	717 (73.5%)	1427(76.8%)	497 (80.8%)	2641 (76.6%)	231 (54.0%)	187 (63.2%)	97 (66.0%)
Worsened	87 (14.6%)	192 (19.7%)	313 (16.9%)	86 (14.0%)	591 (17.1%)	183 (42.8%)	86 (29.1%)	42 (28.6%)
Global Clinical Assessment of Akathisia Score								
N evaluated at BL	597	976	1857	615	3348	428	296	147
N (%) Absent at BL	432 (72.4%)	714 (73.2%)	1393 (75.0%)	465 (75.6%)	2572 (74.6%)	300 (70.1%)	188 (63.5%)	101 (68.7%)
N evaluated at worst value	597	976	1857	615	3348	428	296	147
Change from baseline to worst value:								
Improved	53 (8.9%)	84 (8.6%)	146 (7.9%)	60 (9.8%)	290 (8.4%)	17 (4.0%)	30 (10.1%)	7 (4.8%)
No Change	436 (73.0%)	67 (68.6%)	1319(71.0%)	449 (73.0%)	2438 (70.7%)	194 (45.3%)	168 (56.8%)	95 (64.6%)
Worsened	108(18.1%)	222 (22.7%)	392 (21.1%)	106(17.2%)	720 (20.9%)	217 (50.7%)	98 (33.1%)	45 (30.6%)

Data Source: ISS Table 19.1.1 and ISS Table 19.2.1

Table includes data from all phases of Studies 2001, 2301 (DLP 10 NOV 2014), 3000, 3001, 3002, 3003, 3004, 3005, 3101, US01 and period 1 of Study 2328.

BL=baseline; Comb=combined; HAL=haloperidol; ILO=iloperidone; RIS=risperidone; ZIP=ziprasidone

The Barnes Akathisia Scale (BAS) was not administered in Study 3000; therefore patients from Study 3000 are not represented in these tabulations.

Baseline is defined as the last non-missing evaluation preceding the first dose of study medication.

Percentages are based on the total number of patients within each treatment group at each time point.

Rash, Steven-Johnson's Syndrome and Phototosensitivity Reactions

The frequency of rash was similar across treatment groups. No serious rash events were observed in the clinical trials.

Serious adverse event and deaths

Deaths

Overall Incidence of Deaths

Irrespective of relationship to study drug, 26 patients died while participating in the Iloperidone clinical program. Three patients (2 ILO and 1 RIS) died while enrolled in Study 3007P2, which is not included in the ISS.

The 4 remaining deaths not captured in the ISS database comprised those patients who died either prior to receiving study drug or prior to randomization (2 in Study ILP3000, 1 in Study ILP3004 and 1 in Study ILP3007P2 and 1 from Study 3101 OLE). Two deaths were considered to be "possibly" related to treatment. The first event was a sudden death of unknown cause in patient 056-1012 who received Iloperidone 16 mg/day for 5 months in Study 3002 (ILP3002 056-1012). No autopsy was performed. The second event was a sudden death of probable cardiac arrhythmia based on an autopsy without clear cause of death. This patient had a normal ECG on the day prior to her death.

Adverse Events leading to death, safety database:

Preferred Term	Placebo (N=837)	ILO Comb. (N=4078)	HAL 5-20 mg/d (N=546)	RIS 4-8 mg/d (N=358)	ZIP 160 mg/d (N=184)
Total N who died	*1*	*18*	*1*	*2*	*0*
Alcohol poisoning		1			
Arrhythmia		1			
Cardiac failure		1			
Cardio-respiratory failure	1				
Diabetes mellitus		1			
Pneumonia		1			
Pylorus occlusion		1			
Renal failure		1		1	
Septicemia		1			
Struck by automobile		1			
Sudden cardiac arrest		1			
Sudden death		2			
Cardio-respiratory failure Unknown		1			
Suicide		4	1		
Undetermined etiology/natural causes				1	
Volvulus		1			

Data Source: Studies 2001, 3000, 3001, 3002, 3003, 3004, 3005, 3007, 3101, 2328, 2301, US01 and ISS Listing 1.
AE=adverse event; HAL=haloperidol; ILO Comb.=combined iloperidone; RIS=risperidone; ZIP=ziprasidone.

The total number of sudden deaths or deaths due to cardiac AE from the clinical program is 6.

Mortality Analysis

A mortality analysis was conducted based on patient-years of exposure for the integrated Phase 2/3 Iloperidone clinical studies in the safety database, including deaths during treatment or within 30 days of treatment discontinuation.

Mortality rate for Study Group 1 integrated clinical studies in comparison to select marketed antipsychotics, updated safety data:

Study Drug	Total No. of Patients	Patient-Years of Exposure	Total No. of Deaths	Number of Deaths ≤30 Days [e]	Study Mortality Rate	Mortality per 100 Patient-Years (95% Confidence Intervals)
Iloperidone	4540	2529.79	16	16	0.004	0.63 (0.36, 1.03)
Placebo	737	73.88	1	1	0.001	1.35 (0.03, 7.54)
Haloperidol	546	261.57	1	1	0.002	0.38 (0.01, 1.94)
Risperidone	311	56.30	1	1	0.003	1.78 (0.04, 8.99)
Ziprasidone	184	10.09	0	0	0	0.0 (0.00, 36.57)
Comb. active comparators [a]	1041	327.96	2	2	0.002	0.61 (0.07, 2.00)
Ziprasidone [b]	4571	1732.6	50	28	0.006	1.62 (1.07, 2.34)
Quetiapine [c]	2387	865.3	8	8	0.003	0.92 (0.40, 1.82)
Aripiprazole [d]	4710	2656.3	61	NA	0.013	2.30 (1.76, 2.96)

Table includes data from all phases of Studies 2001, 3000, 3001, 3002, 3003, 3004, 3005, 3101, 2301, US01 and period 1 of Study 2328.
Comb = combined; NA = not available
[a] Data include deaths in the combined haloperidol, risperidone, and ziprasidone groups from the iloperidone clinical development program
[b] Zirpasidone NDA 20-825 FDA Medical Review, part 1, pages 3-4
[c] Quetiapine NDA 20-639 FDA Medical Review, Table 8.1.1.2, page 130
[d] Aripiprazole NDA 21-436 FDA Clinical Review
[e] Includes deaths during treatment or within 30 days of treatment discontinuation

Serious Adverse Events

Overall, in Study Group 1, serious adverse events were reported in 15.2% of Iloperidone-treated patients. This was higher than that observed for the other treatment groups (1.1% to 10.3%), except for haloperidol, which had a similar frequency (16.1%).

Serious Adverse Events in 0.5% or more of patients in any group, Study Group 1 (safety population):

SOC Preferred Term	Placebo (N=737)	ILO 4-8 mg/d (N=1311)	ILO 10-16 mg/d (N=2384)	ILO 20-24 mg/d (N=845)	ILO Comb. (N=4540)	HAL 5-20 mg/d (N=546)	RIS 4-8 mg/d (N=311)	ZIP 160 mg/d (N=184)
Pts with any TEAEs	*495 (67.2%)*	*1067 (81.4%)*	*1952 (81.9%)*	*699 (82.7%)*	*3718 (81.9%)*	*503 (92.1%)*	*252 (81.0%)*	*160 (87.0%)*
Total n serious TEAE	*61*	*307*	*577*	*76*	*960*	*126*	*39*	*2*
Pts with serious TEAE	*53(7.2%)*	*230 (17.5%)*	*399 (16.7%)*	*59 (7.0%)*	*688 (15.2%)*	*88 (16.1%)*	*32 (10.3%)*	*2 (1.1%)*
Nervous system disorders	**3 (0.4%)**	**16 (1.2%)**	**22 (0.9%)**	**3 (0.4%)**	**41 (0.9%)**	**13 (2.4%)**	**6 (1.9%)**	**0**
Akathisia	0	2 (0.2%)	1 (0.0%)	0	3 (0.1%)	7 (1.3%)	1 (0.3%)	0
Tremor	0	0	1 (0.0%)	0	1 (0.0%)	6 (1.1%)	1 (0.3%)	0
Psychiatric disorders	**43 (5.8%)**	**177 (13.5%)**	**321 (13.5%)**	**45 (5.3%)**	**543 (12.0%)**	**68 (12.5%)**	**23 (7.4%)**	**2 (1.1%)**
Schizophrenia	21 (2.8%)	61 (4.7%)	118 (4.9%)	19 (2.2%)	198 (4.4%)	13 (2.4%)	10 (3.2%)	0
Psychotic disorder	9 (1.2%)	46 (3.5%)	108 (4.5%)	18 (2.1%)	172 (3.8%)	21 (3.8%)	5 (1.6%)	2 (1.1%)
Suicidal ideation	3 (0.4%)	10 (0.8%)	20 (0.8%)	3 (0.4%)	33 (0.7%)	4 (0.7%)	3 (1.0%)	0
Anxiety	3 (0.4%)	12 (0.9%)	18 (0.8%)	0	30 (0.7%)	9 (1.6%)	3 (1.0%)	0
Agitation	3 (0.4%)	11 (0.8%)	21 (0.9%)	1 (0.1%)	33 (0.7%)	5 (0.9%)	0	0
Delusion	0	7 (0.5%)	19 (0.8%)	0	26 (0.6%)	2 (0.4%)	1 (0.3%)	0
Depression	1 (0.1%)	7 (0.5%)	15 (0.6%)	2 (0.2%)	24 (0.5%)	5 (0.9%)	0	0
Suicide attempt	0	8 (0.6%)	11 (0.5%)	2 (0.2%)	21 (0.5%)	4 (0.7%)	1 (0.3%)	0
Hallucination, auditory	1 (0.1%)	6 (0.5%)	3 (0.1%)	0	9 (0.2%)	1 (0.2%)	0	0

Data Source: ISS Table 7.5.1
Table includes data from all phases of Studies 2001, 2301 (DLP 10 Nov 2014), 3000, 3001, 3002, 3003, 3004, 3005, 3101, US01 and period 1 of 2328.
HAL=haloperidol; ILO=iloperidone; RIS=risperidone; TEAE=treatment-emergent adverse event; ZIP=ziprasidone.
Patients who experienced multiple Adverse events within the same SOC were counted only once for that same SOC.
Patients who experienced the same AE multiple times within the same SOC were counted only once for the corresponding Preferred Term.
Adverse events are sorted alphabetically by SOC and within each SOC the preferred term is presented by decreasing order of frequency in the combined iloperidone group.
Percentages are based on the total number of patients within each treatment/dose group.

Laboratory findings

Cardiac safety and QT

Preclinical studies have shown that Iloperidone may have the potential to affect cardiac conduction.

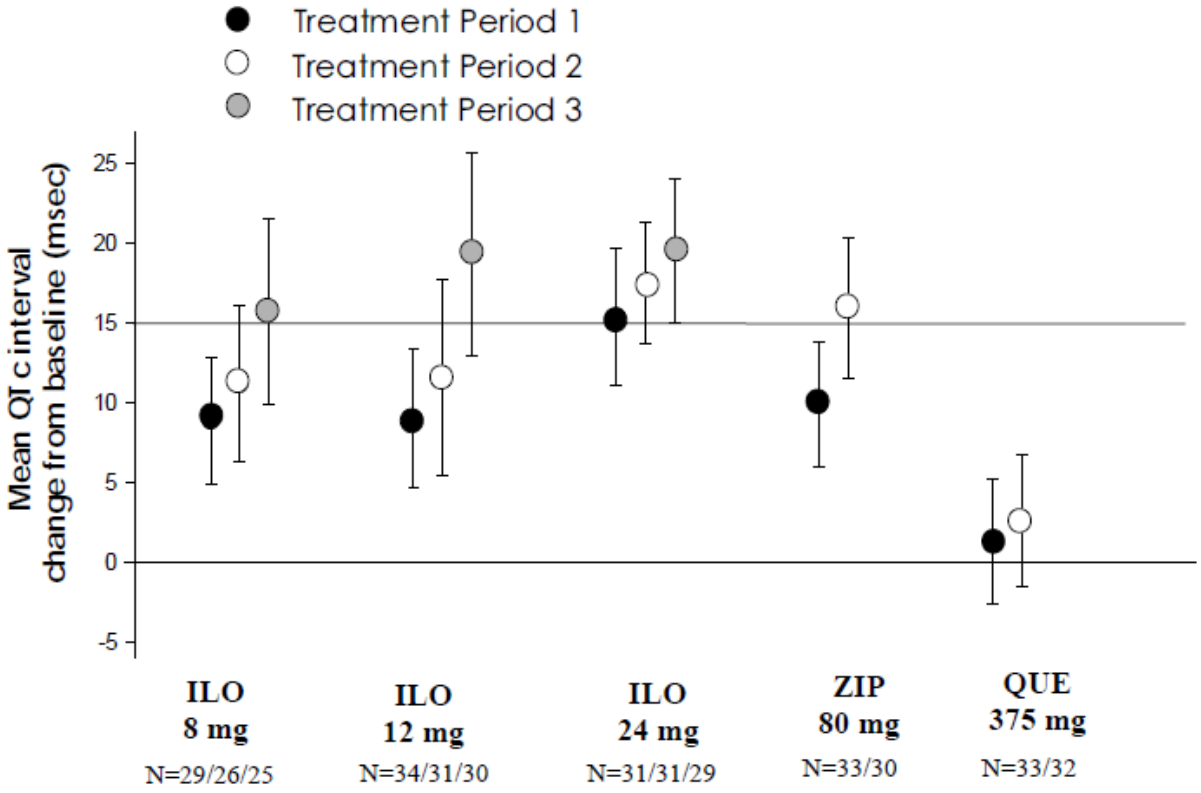
A thorough QT study, study 2328, was conducted to evaluate the potential effects of steady-state concentrations of Iloperidone on QT prolongation in patients with schizophrenia.

Patients were randomly assigned to receive Iloperidone (ILO) 8 mg BID, ILO 12 mg BID (the maximum recommended therapeutic dose), ILO 24 mg QD, ziprasidone 80 mg BID (positive control) or quetiapine 375 mg BID (negative control) in the absence and presence of metabolic inhibition. Changes in QTc were measured at Tmax.

There were 3 treatment periods: Treatment Period 1 (dose titration and steady state without metabolic inhibition), Treatment Period 2 (addition of 1 metabolic inhibitor i.e. a strong CYP2D6 inhibitor), and Treatment Period 3 (addition of a second metabolic inhibitor to the Iloperidone groups i.e. a strong CYP2D6 plus a strong CYP3A4 inhibitor).

Iloperidone 8 mg b.i.d. and 12 mg b.i.d. caused a QTcF prolongation, which was similar to that of the positive control ziprasidone 80 mg b.i.d. The increase in QTcF was dose dependant. QTcF increases further when the two major metabolic pathways CYP2D6 and CYP3A4 for Iloperidone are inhibited. Further, 10% had and an increase in QTc from baseline of ≥ 60 msec.

Mean QTc (Fridericia) Change (95%CI) from baseline to steady state at TMAX during Treatment Periods 1, 2, and 3 (Secondary QTc Population).*



ILO=iloperidone; ZIP=ziprasidone; QUE=quetiapine
P1=Period 1, P2=Period 2, P3=Period 3
Note: * T_{MAX} = estimated time of maximum concentration (ILO=2-4 hours post-dose; ZIP=5-7 hours post-dose; QUET= 1-2.5 hours post-dose)
Source: Figure 9.2-1

Number (%) of patients with QTc increase from baseline to steady state at TMAX of > 30 and 60 msec during Treatment Periods 1, 2, and 3 (Secondary QTc population):*

	ILO 8 mg b.i.d.		ILO 12 mg b.i.d.		ILO 24 mg q.d.		ZIP 80 mg b.i.d.		QUET 375 mg b.i.d.	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Treatment Period 1										
Increase ≥ 30 msec										
Fridericia	29	9 (31)	34	15 (44)	31	19 (61)	33	17 (52)	33	4 (12)
Baseline	29	9 (31)	34	15 (44)	31	19 (61)	33	14 (42)	33	5 (15)
FDA	29	11 (38)	34	15 (44)	31	21 (68)	33	15 (45)	33	7 (21)
Bazett	29	21 (72)	34	21 (62)	31	26 (84)	33	20 (61)	33	18 (55)
Increase ≥ 60 msec										
Fridericia	29	1 (3)	34	0 (0)	31	1 (3)	33	0 (0)	33	0 (0)
Baseline	29	1 (3)	34	0 (0)	31	1 (3)	33	0 (0)	33	0 (0)
FDA	29	1 (3)	34	1 (3)	31	1 (3)	33	0 (0)	33	0 (0)
Bazett	29	1 (3)	34	3 (9)	31	4 (13)	33	5 (15)	33	1 (3)
Treatment Period 2										
Increase ≥ 30 msec										
Fridericia	26	14 (54)	31	15 (48)	31	22 (71)	30	18 (60)	32	6 (19)
Baseline	26	13 (50)	31	15 (48)	31	22 (71)	30	19 (63)	32	6 (19)
FDA	26	14 (54)	31	13 (42)	31	22 (71)	30	19 (63)	32	7 (22)
Bazett	26	17 (65)	31	13 (42)	31	21 (68)	30	23 (77)	32	21 (66)
Increase ≥ 60 msec										
Fridericia	26	1 (4)	31	0 (0)	31	1 (3)	30	0 (0)	32	0 (0)
Baseline	26	1 (4)	31	0 (0)	31	1 (3)	30	0 (0)	32	0 (0)
FDA	26	1 (4)	31	0 (0)	31	0 (0)	30	0 (0)	32	0 (0)
Bazett	26	0 (0)	31	1 (3)	31	1 (3)	30	1 (3)	32	3 (9)
Treatment Period 3										
Increase ≥ 30 msec										
Fridericia	25	13 (52)	30	21 (70)	29	20 (69)	--	--	--	--
Baseline	25	14 (56)	30	20 (67)	29	19 (66)	--	--	--	--
FDA	25	14 (56)	30	20 (67)	29	19 (66)	--	--	--	--
Bazett	25	14 (56)	30	20 (67)	29	19 (66)	--	--	--	--
Increase ≥ 60 msec							--	--	--	--
Fridericia	25	1 (4)	30	3 (10)	29	0 (0)	--	--	--	--
Baseline	25	1 (4)	30	3 (10)	29	0 (0)	--	--	--	--
FDA	25	1 (4)	30	3 (10)	29	0 (0)	--	--	--	--
Bazett	25	2 (8)	30	5 (17)	29	1 (3)	--	--	--	--

N=number of patients; ILO=iloperidone; ZIP=ziprasidone; QUET=quetiapine
*T_{MAX}=estimated time of maximum concentration (ILO = 2-4 hours post-dose; ZIP = 5-7 hours post-dose; QUET = 1-2.5 hours post-dose).
Each patient is counted once within each steady state if he/she had at least one QTc increase ≥30 msec or ≥60 msec from baseline.
Source: Post-text Table 9.2.1-3

No death case was reported. Some patients presented symptomatic events associated with the QTc prolongations: one patient developed palpitation in a setting of a bradycardia, hypotension then " presyncope" associated with QTc increase ≥ 60ms. For 10 other cases, the clinical events reported together with QTc prolongation were tachycardia (6), hypotension (2) and/or bradycardia (2).

Effect of Co-administered Metabolic Inhibitors and CYP2D6 Polymorphisms on the QTc Interval

128 patients enrolled in Study 2328 were genotyped for 2 common *CYP2D6* single-nucleotide polymorphisms (**4* (*1846G>A*) and **10* (*100C>T*; a.k.a. *P34S*) to determine if either is associated with an increased risk for QT prolongation. For the **4* (*1846G>A*) polymorphism, patients with the *AA* variant were identified as poor metabolizers, while those with the *AG* variant had an intermediate phenotype between the poor metabolizer and the wild type. For the **10* (*100C>T*) polymorphism, patients carrying the *TT* variant were identified as poor metabolizers, while those with the *CT* variant had an intermediary phenotype. The wild type alleles were**4* or **10* allele (*GG* or *CC*).

During Treatment Period 1, poor and intermediate metabolizers had larger increases in QTcF interval from baseline following treatment with iloperidone compared with patients who possess the wild-type allele.

Changes from baseline in QTcF interval in patients with select CYP2D6 polymorphisms, Study 2328:

Genotype	No. of Patients	LS Mean QTcF Change from Baseline (msec)	P-value
CYP2D6*4 (1846G>A)			
GG (wildtype)	52	11.1	0.059
nonGG (*GA* or *AA*)	16	18.5	
CYP2D6*10 (100C>T)			
CC (wildtype)	54	10.8	0.028
nonCC (*CT* or *TT*)	17	19.2	

Data Source: CILO522A2328-PG-1
LS=least squares

Table 2: *CYP2D6*4 (G1846A)* polymorphism is association with QTcF change from baseline following iloperidone treatment

Genotype	Number of Patients	LSMeans QTcF Change from Baseline (msec)
GG	52	11.1
GA	14	15.9
AA	2	41.6

Genotype	Number of Patients	LSMeans QTcF Change from Baseline (msec)	P Value
GG	52	11.1	0.0594
nonGG	16	18.5	

Table 3: *CYP2D6*10 (C100T)* polymorphism is association with QTcF change from baseline following iloperidone treatment

Genotype	Number of Patients	LSMeans QTcF Change from Baseline (msec)
CC	54	10.8
CT	14	16.9
TT	3	31.3

Genotype	Number of Patients	LSMeans QTcF Change from Baseline (msec)	P Value
nonCC	54	10.8	0.0281
CC	17	19.2	

In Study 3101, QTcF data were calculated on a subset of patients who had the *CYP2D6*4* (*1846GA* or *AA*) or *CYP2D6*10* (*100CT* or *TT*) polymorphisms. In the Iloperidone group, mean changes in QTcF interval from baseline at Day 14, Day 28 and endpoint were significantly higher in the combined *non-GG* subgroups compared with the *GG* (wildtype) subgroup. There is limited data from homozygotes and does not allow a precise estimate, but it seems to point to a greater effect in these patients.

*Summary of QTcF interval data by CYP2D6*4 genotype polymorphisms, Study 3101 (safety population):*

QTc Parameter	Iloperidone		Ziprasidone		Placebo	
	GG N=227	*non-GG*[a] N=69	*GG* N=111	*non-GG*[a] N=36	*GG* N=118	*non-GG*[a] N=27
Mean QTcF at BL (msec)	388.2	390.6	387.2	389.2	387.2	396.6
Mean QTcF change from BL at Day 14 (msec)[b]	+10.4	+15.0[c]	+11.7	+9.3	-0.2	-2.4
Mean QTcF change from BL at Day 28 (msec)[b]	+5.0	+12.9[d]	+6.0	+5.1	-2.2	-5.2
Mean QTcF change from BL at Endpoint (msec)[b]	+5.6	+11.9[e]	+5.7	+6.7	-1.4	-3.6
Mean maximum QTcF change from BL (msec) (min-max)	+14.2 (-72, 68)	+23.6[d] (-31, 53)	+11.5 (-79, 84)	+15.1 (-28, 40)	-1.3 (-73, 45)	-5.5 (-35, 32)
N (%) with change in QTcF from <500 msec at BL to >500 msec post-BL	0	0	0	0	0	0
N (%) with QTcF >500 msec at both BL and post-BL	0	0	0	0	0	0
N (%) with ≥15% increase in QTcF from BL	2 (0.7%)	0	1 (0.7%)	0	0	0

Data Source: Study Report VP-VYV-683-3101 Table 10.5.1-1e through Table 10.5.1-4e
BL=baseline
[a] Non-GG subgroup comprised of *CYP2D6*4 (1846G>A) GA* and *AA* genotypes combined
[b] Number of patients with postbaseline data varied at each time point
P-values based on ANCOVA comparing ILO *CYP2D6*4 (1846G>A) GG* vs *non-GG* genotype groups. Model includes phenotype and Baseline (as a covariate)
[c] p=0.008 [d] p=0.002 [e] 0.009

QTc Evaluation in the Phase 3 Clinical Program

ECGs were performed for more than 85% of patients across all treatment groups in Study Group 1, albeit not necessarily at the same time of day or the same time after receiving a dose of study drug.

Outlier Analyses of Changes in QTc Interval

In both the 4-8 mg/day and 10-16 mg/day Iloperidone group approximately 5% had a ≥ 60 msec. increase in QTcF at some point during treatment.

Maximum QTcF values - outlier analysis, Study Group 1 (safety population):

QTcF Parameter	Placebo (N=737)	ILO 4-8 mg/d (N=1311)	ILO 10-16 mg/d (N=2384)	ILO 20-24 mg/d (N=845)	ILO Comb. (N=4540)	HAL 5-20 mg/d (N=546)	RIS 4-8 mg/d (N=311)	ZIP 160 mg/d (N=184)
Fridericia's formula								
Mean (±SD) baseline value, msec	388.4 (22.03)	379.2 (23.58)	385.7 (26.04)	393.4 (21.12)	385.4 (24.95)	375.8 (23.98)	378.8 (22.59)	386.9 (17.22)
Mean (±SD) maximum value, msec	387.1 (24.08)	387.6 (28.55)	396.1 (29.23)	404.0 (26.20)	395.3 (29.02)	380.7 (29.37)	382.6 (25.17)	398.8 (24.49)
N (%) with QTc:								
≥450 msec, all patients	6 (0.9%)	20 (1.7%)	80 (3.5%)	37 (4.5%)	137 (3.2%)	6 (1.1%)	1 (0.4%)	4 (2.2%)
≥450 msec, females	4 (1.7%)	17 (3.9%)	47 (5.7%)	21 (9.7%)	85 (5.8%)	4 (2.1%)	1 (1.1%)	4 (8.7%)
≥450 msec, males	2 (0.4%)	3 (0.4%)	33 (2.3%)	16 (2.7%)	52 (1.9%)	2 (0.6%)	0	0
≥480 msec, all patients	0	2 (0.2%)	8 (0.4%)	3 (0.4%)	13 (0.3%)	1 (0.2%)	0	0
≥480 msec, females	0	2 (0.5%)	3 (0.4%)	3 (1.4%)	8 (0.5%)	1 (0.5%)	0	0
≥480 msec, males	0	0	5 (0.3%)	0	5 (0.2%)	0	0	0
≥500 msec, all patients	0	0	3 (0.1%)	0	3 (0.1%)	0	0	0
≥500 msec, females	0	0	0	0	0	0	0	0
≥500 msec, males	0	0	3 (0.2%)	0	3 (0.1%)	0	0	0
N (%) with ≥15% increase from BL in QTc at any TP	7 (1.0%)	76 (6.5%)	157 (6.9%)	24 (2.9%)	257 (6.0%)	33 (6.2%)	10 (3.6%)	3 (1.6%)
N (%) with ≥30 msec change in QTc at any TP	65 (9.3%)	359 (30.5%)	745 (32.7%)	197 (24.1%)	1301 (30.5%)	167 (31.5%)	47 (16.8%)	42 (23.1%)
N (%) with ≥60 msec change in QTc at any TP	4 (0.6%)	58 (4.9%)	118 (5.2%)	15 (1.8%)	191 (4.5%)	18 (3.4%)	7 (2.5%)	3 (1.6%)

Data Source: ISS Table 17.6.1. Note that ISS Table 17.6.1 omits a parameter if there were no occurrences for that particular parameter in any treatment group. Table includes data from all phases of Studies 2001, 2301 (DLP 10 NOV 2014), 3000, 3001, 3002, 3003, 3004, 3005, 3101, US01 and period 1 of Study 2328
BL=baseline; Comb=combined; HAL=haloperidol; ILO=iloperidone; RIS=risperidone; TP=time point; ZIP=ziprasidone

QTc Interval ≥500 msec: Three males and no females had a QTcF interval ≥500 msec. Two events occurred during the open-label treatment phase. For one patient, the QTc prolongation (507 msec) was associated with an extreme overdose of Iloperidone (438 mg taken over a 4-day period). No cardiac adverse event occurred and the patient fully recovered. The second patient experienced QTc prolongation while being treated in the ICU for septic shock 3 days' post treatment; he subsequently died of sepsis. The third patient experienced prolonged QTc and worsening hypertension at Day 7 without additional clinical symptoms. The QTc prolongation resolved upon discontinuation of Iloperidone without any residual effects. Using Bazett's formula, one additional patient, a female also receiving open-label Iloperidone, had a QTcB interval ≥500 msec, 272 days after treatment initiation.

ECG Abnormalities During Iloperidone Treatment, Phase 3 Studies

Overall, ECG abnormalities occurred more frequently in the Iloperidone combined group than the other treatment groups.

Incidence of new or worsening ECG abnormalities during treatment in ≥ 1% of patients in any treatment group, Study Group 1 (safety population):

Preferred Term Number (%) of patients with:	Placebo (N=737)	ILO Comb. (N=4540)	HAL 5-20 mg/d (N=546)	RIS 4-8 mg/d (N=311)	ZIP 160 mg/d (N=184)
Total n (%) who had an ECG	697 (94.6%)	4271 (94.1%)	531 (97.3%)	279 (89.7%)	182 (98.9%)
Total n (%) with new or worse ECG abnormality	177 (25.4%)	1712 (40.1%)	177 (33.3%)	79 (28.3%)	58 (31.9%)
Sinus Tachycardia	64 (9.1%)	720 (16.9%)	85 (16.0%)	53 (19.0%)	24 (13.2%)
Other Morphology	23 (3.3%)	170 (4.0%)	0	0	0
Sinus Bradycardia	3 (0.4%)	122 (2.9%)	22 (4.1%)	3 (1.1%)	0
Other Arrhythmia	22 (3.2%)	117 (2.7%)	0	0	0
T Waves: Flat	12 (1.7%)	100 (2.3%)	11 (2.1%)	10 (3.6%)	20 (11.1%)
First Degree AV Block	14 (2.0%)	118 (2.8%)	20 (3.8%)	8 (2.9%)	2 (1.1%)
APC	4 (0.6%)	97 (2.3%)	9 (1.7%)	2 (0.7%)	0
Short PR	4 (0.6%)	87 (2.0%)	16 (3.0%)	5 (1.8%)	0
Prolonged QTc	4 (0.6%)	85 (2.0%)	0	0	0
Other T Waves	10 (1.4%)	67 (1.6%)	0	0	0
VPC	2 (0.3%)	66 (1.5%)	6 (1.1%)	3 (1.1%)	0
ST Segment: Depressed	4 (0.6%)	52 (1.2%)	12 (2.3%)	2 (0.7%)	4 (2.2%)
T Waves: Inverted	8 (1.1%)	46 (1.1%)	4 (0.8%)	2 (0.7%)	7 (3.8%)
T Waves: Biphasic	1 (0.1%)	24 (0.6%)	4 (0.8%)	0	3 (1.6%)
Left Anterior Hemiblock	1 (0.1%)	20 (0.5%)	1 (0.2%)	3 (1.1%)	0

Data Source: ISS Table 17.8.1
Table includes data from all phases of Studies 2001, 3000, 3001, 3002, 3003, 3004, 3005, 3101, 2301, US01 and period 1 of Study 2328 (treatment without metabolic inhibitors).
Comb=combined; HAL=haloperidol; ILO=iloperidone; LAH=left anterior hemiblock; RIS=risperidone; ZIP=ziprasidone
Patients experiencing the same Specific Diagnosis multiple times will only be counted once for the corresponding diagnosis.
Specific Diagnoses are presented by decreasing order of total frequency in the Combined Iloperidone Group.
Percentages for the total number of patients with ECG are based on the total number of subjects in treatment/dose group. All other percentages are based on the total number of patients who had an ECG.

Cardiovascular Adverse Events

Cardiac adverse event occurred more frequently in the Iloperidone combined group and the ziprasidone group compared to the other treatment groups. However, more patients discontinued, had a dose reduction/interruption or died due to a cardiac adverse event in the Iloperidone groups than in the ziprasidone group.

Safety profile for cardiovascular Adverse Events, Study Group 1 (safety population):

Number (%) of patients with:	Placebo (N=737)	ILO Comb. (N=4540)	HAL 5-20 mg/d (N=546)	RIS 4-8 mg/d (N=311)	ZIP 160 mg/d (N=184)
Cardiac AE	24 (3.3%)	412 (9.1%)	23 (4.2%)	11 (3.5%)	20 (10.9%)
Severe cardiac AE	2 (0.3%)	31 (0.7%)	3 (0.5%)	1 (0.3%)	1 (0.5%)
Drug-related cardiac AE	13 (1.8%)	275 (6.1%)	12 (2.2%)	5 (1.6%)	16 (8.7%)
Serious cardiac AE	4 (0.5%)	18 (0.4%)	1 (0.2%)	0	0
Serious drug-related cardiac AE	3 (0.4%)	12 (0.3%)	0	1 (0.3%)	0
Dose reduction/interruption	3 (0.4%)	40 (0.9%)	3 (0.5%)	0	1 (0.5%)
Tx discontinued for cardiac AE	3 (0.4%)	69 (1.5%)	2 (0.4%)	2 (0.6%)	1 (0.5%)
Death due to cardiac AE	1 (0.0%)	3 (0.0%)[a]	0	0	0

Data Source: ISS Table 7.5.1, ISS Table 21.1.1, ISS Table 21.2.1, ISS Table 21.3.1, ISS Table 21.4.1, ISS Table 21.5.1, ISS Table 21.6.1, ISS Table 21.7.1, ISS Table 21.8.1 and ISS Listing 1.

Table includes data from all phases of Studies 2001, 2301 (DLP of 10 NOV 2014), 3000, 3001, 3002, 3003, 3004, 3005, 3101, US01 and period 1 of 2328.

Comb=combined; HAL=haloperidol; ILO=iloperidone; RIS=risperidone; ZIP=ziprasidone

[a] Includes 2 cardiac-related sudden deaths (ILP3003 533-1006 and ILP3005 976-1002).

Frequency of abnormal changes in pulse rate, Study Groups 1, 2 and 3 (safety population):

Pulse Rate Assessment	Placebo	ILO 4-8 mg/d	ILO 10-16 mg/d	ILO 20-24 mg/d	ILO Comb.	HAL 5-20 mg/d	RIS 4-8 mg/d	ZIP 160 mg/d
Study Group 1								
Number of patients [a]	**692 (93.9%)**	**1269 (96.8%)**	**2254 (94.5%)**	**748 (88.5%)**	**4271 (94.1%)**	**545 (99.8%)**	**301 (96.8%)**	**149 (81.0%)**
≥120 bpm and an increase of ≥15 bpm [b]	341 (5.9%)	354(27.9%)	510 (22.6%)	173 (23.1%)	1037 (24.3%)	104 (19.1%)	72 (23.9%)	16 (10.7%)
≤50 bpm and a decrease of ≥15 bpm [b]	6 (0.9%)	28 (2.2%)	52 (2.3%)	9 (1.2%)	89 (2.1%)	16 (2.9%)	7 (2.3%)	3 (2.0%)
Study Group 2								
Number of patients [a]	**581 99.0%)**	**460 (97.9%)**	**481 (99.6%)**	**391 (100.0%)**	**1332 (99.1%)**	**118 (100.0%)**	**302 (98.7%)**	**149 (99.3%)**
≥120 bpm and an increase of ≥15 bpm [b]	39 (6.7%)	146 (31.7%)	111 (23.1%)	132 (33.8%)	389 (29.2%)	21 (17.8%)	66 (21.9%)	15 (10.1%)
≤50 bpm and a decrease of ≥15 bpm [b]	5 (0.9%)	2 (0.4%)	8 (1.7%)	2 (0.5%)	12 (0.9%)	0	5 (1.7%)	3 (2.0%)
Study Group 3								
Number of patients [a]	**695 (94.3%)**	**952 (98.6%)**	**1500 (98.7%)**	**419 (97.4%)**	**2871 (98.5%)**	**545 (99.8%)**	**301 (98.4%)**	**149 (99.3%)**
≥120 bpm and an increase of ≥15 bpm [b]	43 (6.2%)	307 (32.2%)	464 (30.9%)	138 (32.9%)	909 (31.7%)	104 (19.1%)	72 (23.9%)	20 (13.4%)
≤50 bpm and a decrease of ≥15 bpm [b]	6 (0.9%)	16 (1.7%)	44 (2.9%)	2 (0.5%)	62 (2.2%)	16 (2.9%)	7 (2.3%)	3 (2.0%)

Data source: ISS Table 15.5.1, ISS Table 15.5.2, ISS Table 15.5.3

Table includes data from all phases of studies 2001, 2301 (DLP 10 NOV 2014), 3000, 3001, 3002, 3003, 3004, 3005, 3101, US01 and period 1 of Study 2328

bpm=beats per minute; Comb=combined; HAL=haloperidol; ILO=iloperidone; RIS=risperidone; ZIP=ziprasidone.

a Number of patients with at least on postbaseline vital signs assessment.

b Percentages are based on the total number of observed patients within each treatment group.

Blood Pressure

Frequency of abnormal changes in blood pressure, Study Group 1 (safety population):

Blood Pressure Parameter	Placebo (N=737)	ILO 4-8 mg/d (N=1311)	ILO 10-16 mg/d (N=2384)	ILO 20-24 mg/d (N=845)	ILO Comb. (N=4540)	HAL 5-20 mg/d (N=546)	RIS 4-8 mg/d (N=311)	ZIP 160 mg/d (N=184)
Patients With at Least 1 Postbaseline Assessment [a]	692 (93.9%)	1269 (96.8%)	2254 (94.5%)	748 (88.5%)	4271 (94.1%)	545 (99.8%)	301 (96.8%)	149 (81.0%)
Systolic Blood Pressure (mm Hg) [b]								
>=150 mm Hg and an increase of >=10 mm Hg	121 (17.5%)	256 (20.2%)	373 (16.5%)	100 (13.4%)	729 (17.1%)	127 (23.3%)	78 (25.9%)	30 (20.1%)
<=90 mm Hg and a decrease of >=10 mm Hg	50 (7.2%)	389 (30.7%)	614 (27.2%)	104 (13.9%)	1107 (25.9%)	179 (32.8%)	39 (13.0%)	12 (8.1%)
Diastolic Blood Pressure (mm Hg) [b]								
>=100 mm Hg	108 (15.6%)	243 (19.1%)	357 (15.8%)	46 (6.1%)	46 (6.1%)	176 (32.3%)	61 (20.3%)	26 (17.4%)
<=65 mm Hg	305 (44.1%)	860 (67.8%)	1385 (61.4%)	386 (51.6%)	386 (51.6%)	394 (72.3%)	157 (52.2%)	61 (40.9%)
>=100 mm Hg and an increase of >=10 mm Hg	87 (12.6%)	206 (16.2%)	321 (14.2%)	38 (5.1%)	38 (5.1%)	163 (29.9%)	50 (16.6%)	22 (14.8%)
<=65 mm Hg and a decrease of >=10 mm Hg	233 (33.7%)	748 (58.9%)	1212 (53.8%)	318 (42.5%)	318 (42.5%)	349 (64.0%)	133 (44.2%)	42 (28.2%)

Data Source: ISS Table 15.5.1
Table includes data from all phases of studies 2001, 2301 (DLP 10 NOV 2014), 3000, 3001, 3002, 3003, 3004, 3005, 3101, US01 and period 1 of Study 2328
Comb=combined; HAL=haloperidol; ILO=iloperidone; RIS=risperidone; ZIP=ziprasidone.
[a]Percentages are based on the total number of patients within each treatment group.
[b]Percentages are based on the total number of observed patients within each treatment group.

Orthostatic hypotension was most commonly associated with dizziness. Syncope occurred in 4 patients: one each in the placebo, ILO 4-8 mg/day, ILO 10-16 mg/day, and ILO 20-24 mg/day groups.

Frequency of orthostatic hypotension over all studies, Study Group 1 (safety population):

Vital Signs	Placebo (N=737)	ILO 4-8 mg/d (N=1311)	ILO 10-16 mg/d (N=2384)	ILO 20-24 mg/d (N=845)	ILO Comb. (N=4540)	HAL 5-20 mg/d (N=546)	RIS 4-8 mg/d (N=311)	ZIP 160 mg/d (N=184)
Patients with at Least 1 Postbaseline Assessment [a]	692 (93.9%)	1269 (96.8%)	2254 (94.5%)	748 (88.5%)	4271 (94.1%)	545 (99.8%)	301 (96.8%)	149 (81.0%)
Patients with Orthostatic Response [b]	44 (6.4%)	216 (17.0%)	297 (13.2%)	67 (9.0%)	580 (13.6%)	64 (11.7%)	40 (13.3%)	3 (2.0%)
Patients with Sustained Orthostasis [b]	0	16 (1.3%)	39 (1.7%)	7 (0.9%)	62 (1.5%)	4 (0.7%)	0	0 (0.0%)

Data Source: ISS Table 15.3.1
Table includes data from all phases of studies 2001, 2301 (DLP 10 NOV 2014), 3000, 3001, 3002, 3003, 3004, 3005, 3101, US01 and period 1 of Study 2328
Comb=combined; HAL=haloperidol; ILO=iloperidone; RIS=risperidone; ZIP=ziprasidone.
[a]Percentages are based on the total number of patients within each treatment group.
[b]Percentages are based on the total number of observed patients within each treatment group.

Body Weight

For Study Group 1, a dose-related increase in mean weight from baseline was observed in Iloperidone-treated patients. Approximately 30% of Iloperidone-treated patients had a weight gain of 7% or more.

Summary of weight changes, Study Group 1 (safety population):

Weight (kg) Time point	Placebo (N=737)	ILO 4-8 mg/d (N=1311)	ILO 10-16 mg/d (N=2384)	ILO 20-24 mg/d (N=845)	ILO Comb. (N=4540)	HAL 5-20 mg/d (N=546)	RIS 4-8 mg/d (N=311)	ZIP 160 mg/d (N=184)
Baseline Weight: n	725	1272	2319	782	4373	541	303	152
Mean	80.7	76.5	77.1	78.3	78.3	72.2	82.1	81.4
(SD)	(20.55)	(19.11)	(20.79)	(21.21)	(20.59)	(20.19)	(20.00)	(17.69)
Postbaseline Weight Change: n, Mean (SD)								
Week 1	497 0.1 (2.14)	939 0.7 (2.43)	1681 0.6 (3.11)	543 1.1 (2.06)	3163 0.7 (2.77)	480 -0.2 (1.72)	252 0.9 (2.27)	134 0.6 (1.90)
Week 4	444 0.3 (2.97)	662 1.6 (3.25)	1483 1.3 (3.05)	488 2.3 (3.34)	2633 1.6 (3.18)	389 0.0 (3.56)	211 1.6 (3.54)	98 1.4 (2.86)
Week 6	185 -0.3 (3.78)	542 2.1 (3.79)	1220 1.6 (3.96)	255 2.0 (3.56)	2017 1.8 (3.87)	338 0.3 (3.19)	185 1.8 (3.84)	0
6 Wks - 3 Mos (inclusive)	130 0.8 (3.78)	637 2.1 (4.51)	1601 1.9 (4.55)	443 1.8 (5.55)	2681 1.9 (4.72)	333 0.7 (3.95)	96 2.2 (4.32)	0
3 Mos - 6 Mos (inclusive)	51 0.6 (4.84)	535 2.7 (6.30)	1176 2.7 (5.69)	245 1.8 (4.91)	1956 2.6 (5.78)	282 1.2 (5.51)	45 3.4 (7.27)	0
6 Mos - 12 Mos (inclusive)	17 0.1 (6.43)	409 3.0 (8.81)	861 3.1 (7.96)	119 1.5 (6.78)	1389 2.9 (8.14)	232 1.9 (6.89)	36 4.6 (11.38)	0
>12 Months	0	236 3.2 (10.28)	479 2.9 (8.91)	46 0.8 (7.27)	761 2.8 (9.27)	19 1.0 (5.24)	3 -1.4 (11.16)	0
Endpoint (mean change)	725 0.1 (3.24)	1272 1.5 (6.45)	2319 1.9 (6.54)	782 2.0 (5.37)	4373 1.8 (6.32)	541 0.8 (5.41)	303 1.7 (5.33)	152 1.1 (2.82)
Worst Possible Value Decreased	489 -2.56 (2.16)	782 -3.39 (3.96)	1423 -3.40 (4.47)	441 -2.48 (2.93)	2646 -3.24 (4.11)	419 -3.35 (3.73)	175 -2.69 (2.71)	85 -1.72 (1.63)
Worst Possible Value Increased	534 2.67 (3.16)	1011 5.42 (5.88)	1991 5.42 (5.96)	681 4.52 (4.73)	3683 5.25 (5.74)	429 4.20 (4.15)	247 4.41 (4.82)	126 2.68 (1.98)

Weight (kg) Time point	Placebo (N=737)	ILO 4-8 mg/d (N=1311)	ILO 10-16 mg/d (N=2384)	ILO 20-24 mg/d (N=845)	ILO Comb. (N=4540)	HAL 5-20 mg/d (N=546)	RIS 4-8 mg/d (N=311)	ZIP 160 mg/d (N=184)
Distribution of Percent Weight Change								
0-<7%	352 (48.6%)	610 (48.0%)	1077 (46.4%)	428 (54.7%)	2115 (48.4%)	237 (43.8%)	172 (56.8%)	101 (66.4%)
7-<10%	30 (4.1%)	86 (6.8%)	170 (7.3%)	71 (9.1%)	327 (7.5%)	38 (7.0%)	21 (6.9%)	6 (3.9%)
10-<15%	12 (1.7%)	74 (5.8%)	161 (6.9%)	44 (5.6%)	279 (6.4%)	30 (5.5%)	11 (3.6%)	2 (1.3%)
15-<20%	2 (0.3%)	32 (2.5%)	76 (3.3%)	11 (1.4%)	119 (2.7%)	12 (2.2%)	6 (2.0%)	0
>=20%	0	48 (3.8%)	91 (3.9%)	8 (1.0%)	147 (3.4%)	15 (2.8%)	5 (1.7%)	0
>=7% (inclusive)	67 (9.2%)	377 (29.6%)	748 (32.3%)	191 (24.4%)	1316 (30.1%)	140 (25.9%)	64 (21.1%)	11 (7.2%)
Endpoint (% change)	0.3 (4.14)	2.4 (9.29)	2.9 (9.23)	2.5(6.80)	2.7 (8.87)	1.7 (8.44)	2.2 (6.27)	1.4 (3.35)

Data Source: ISS Table 16.1.1, ISS Table 16.2.1, ISS Table 16.3.1

Table includes data from all phases of studies 2001, 2301 (DLP 10 NOV 2014), 3000, 3001, 3002, 3003, 3004, 3005, 3101, US01 and period 1 of Study 2328

Percentages are based on the total number of observed patients within each treatment group.

Elevated Prolactin

The percentages of patients who had a *normal* prolactin value at baseline and an *elevated* prolactin value during treatment are as follows: 4.8%, 16.9%, 71.8%, 91.2% and 10.3% for the placebo, combined Iloperidone, haloperidol, risperidone and ziprasidone groups, respectively.

Glucose

The percentages of patients who had a *normal* glucose value at baseline and an *elevated* glucose value during treatment are as follows: 12.4%, 14.4%, 14.6%, 20.3%, and 10.0% for the placebo, combined Iloperidone, haloperidol, risperidone, and ziprasidone groups, respectively. Glucose concentrations were not measured under fasting conditions in every study.

Changes in glucose concentration in fasting patients show that an excess of approximately 4-5% of the patients developed a glucose level of >7 mmol/L in the Iloperidone combined group compared to placebo or ziprasidone.

Shifts in glucose concentration from grade 0 at baseline to grade 1 or higher during a 4-week treatment period in fasting patients:

	Placebo n=101	ILO 4-8 mg/d n=2	ILO 10-16 mg/d n=6	ILO 20-24 mg/d n=205	ILO Comb. n=213	ZIP 160 mg/d n=113
Grade 0 ≤6.1 mmol/L (≤110 mg/dL)	91 (90.1%)	2 (100%)	4 (66.7%)	172 (83.9%)	178 (83.6%)	100 (88.5%)
Grade 1 >6.1 - 7.0 mmol/L[a]	4 (4.0%)	0	1 (16.7%)	11 (5.4%)	12 (5.6%)	5 (4.4%)
Grade 2 >7.0 – 11.1 mmol/L[a]	6 (5.9%)	0	1 (16.7%)	18 (8.8%)	19 (8.9%)	7 (6.2%)
Grade 3 >11.1 – 27.7 mmol/L (200 mg/dL)	0	0	0	4 (1.9%)	4 (1.0%)	1 (0.9%)
Grade 4 >27.7 mmol/L (≥500 mg/dL)	0	0	0	0	0	0

Data Source: ISS pooled database (Laboratory domain)
Comb=combined; ILO=iloperidone; ZIP=ziprasidone
[a] Grade 1 or 2=126 to 200 mg/dL

The incidence of hyperglycemia was 0.4% and 1.3% for the >6-12-month and >12-month periods, respectively. For the open-label extension phase (Study Group 4), newly emergent hyperglycemia occurred in 16 patients, most commonly after 6 months of treatment (56.25%, n=9 of 16). Eleven of these patients previously received Iloperidone during double-blind treatment while the remaining 5 had previously been treated with risperidone (n=2, 1.7%). Reported adverse events of “hyperglycemia” tended to occur with increased exposure to Iloperidone.

Hematologic Laboratory Evaluations

Few patients in each Iloperidone treatment group had a shift from Grade 0 to Grade 3 or Grade 4 lymphocytopenia or neutropenia.

Clinically Relevant Biochemical Laboratory analysis

Slightly more patients in the Iloperidone combined group compared to placebo went from normal levels to high levels of hepatic transaminase enzymes. Three patients discontinued due to an increase in hepatic transaminases.

Metabolic Function Analytes

There is a slight tendency towards dyslipidemia (cholesterol, LDL and triglycerides).

Mean baseline values and mean changes from baseline in biochemical laboratory analytes, Study Group 1 (safety population):

Laboratory Analyte	Placebo (N=737)	ILO 4-8 mg/d (N=1311)	ILO 10-16 mg/d (N=2384)	ILO 20-24 mg/d (N=845)	ILO Comb. (N=4540)	HAL 5-20 mg/d (N=546)	RIS 4-8 mg/d (N=311)	ZIP 160 mg/d (N=184)
Metabolic Function Analytes								
Cholesterol, Total (mmol/L)								
BL=N, WV=L	8 (1.2%)	4 (0.3%)	33 (1.6%)	14 (1.9%)	51 (1.3%)	0	0	0
BL=N, WV=H	49 (7.4%)	125 (10.8%)	303 (14.2%)	78 (10.5%)	506 (12.5%)	106 (20.3%)	10 (3.6%)	17 (11.7%)
High Density Lipoprotein (mmol/L)								
BL=N, WV=L	13 (6.0%)	0	31 (5.4%)	22 (4.1%)	53 (4.6%)	0	0	6 (4.2%)
BL=N, WV=H	0	0	0	0	0	0	0	0
LDH (U/L)								
BL=N, WV=L	0	0	0	0	0	0	0	0
BL=N, WV=H	8 (1.2%)	9 (1.3%)	13 (1.3%)	6 (1.0%)	28 (1.2%)	4 (3.3%)	3 (1.1%)	0
Low Density Lipoprotein (Calc) (mmol/L)								
BL=N, WV=L	0	0	0	0	0	0	0	0
BL=N, WV=H	0	0	27 (12.8%)	27 (11.7%)	0	0	7 (5.8%)	0
Prolactin (µg/L)								
BL=N, WV=L	4 (0.9%)	4 (0.9%)	11 (1.0%)	1 (0.2%)	16 (0.7%)	1 (0.5%)	0	2 (1.5%)
BL=N, WV=H	20 (4.7%)	77 (17.0%)	167 (15.3%)	102 (17.0%)	346 (16.1%)	136 (70.4%)	71 (88.5%)	13 (9.5%)
Triglycerides (mmol/L)								
BL=N, WV=L	1 (0.2%)	0	6 (0.3%)	5 (0.8%)	11 (0.3%)	0	0	0
BL=N, WV=H	71 (11.5%)	164 (14.5%)	290 (14.8%)	95 (14.6%)	549 (14.7%)	102 (19.6%)	30 (10.8%)	25 (17.2%)

Urine analysis

Many patients in the Iloperidone combined group compared to placebo had bacteriuria and positive urine nitrite.

Safety in special populations

Age Group

28 patients older than 65 years were included the integrated clinical studies. Exposure and safety parameters were analysed by the following age categories: <50 and ≥50 years.

Patients older than 50 years had a slightly higher incidence of adverse events leading to withdrawal. A higher percentage of Iloperidone-treated patients 50 years or older died (0.8%) compared with patients younger than 50 (0.2%). In the comparator groups, all deaths occurred in patients younger than 50.

Safety profile by age, Study Group 1 (safety population):

Total n (%) of patients with:	Placebo (N=737)		ILO Comb. (N=4540)		HAL (N=546)		RIS (N=311)		ZIP (N=184)	
	<50 y (N=620)	≥50 y (N=117)	<50 y (N=3740)	≥50 y (N=800)	<50 y (N=481)	≥50 y (N=65)	<50 y (N=252)	≥50 y (N=59)	<50 y (N=156)	≥50 y (N=28)
Adverse Events[a]	413 (66.6%)	82 (70.1%)	3072 (82.1%)	646 (80.8%)	441 (91.7%)	62 (95.4%)	204 (81.0%)	48 (81.4%)	134 (85.9%)	26 (92.9%)
Drug-related[b]	229 (36.9%)	47 (40.2%)	2041 (54.6%)	443 (55.4%)	348 (72.3%)	38 (58.5%)	130 (51.6%)	25 (42.4%)	115 (73.7%)	26 (92.9%)
Severe[c]	67 (10.8%)	18 (12.0%)	624 (16.7%)	120 (15.0%)	146 (30.4%)	18 (27.7%)	38 (15.1%)	9 (15.3%)	11 (7.1%)	4 (14.3%)
Serious AEs[d]	38 (6.1%)	15 (12.8%)	582 (15.6%)	106 (13.3%)	79 (16.4%)	9 (13.8%)	27 (10.7%)	5 (8.5%)	1 (0.6%)	1 (3.6%)
Drug-related[e]	8 (1.3%)	3 (2.6%)	80 (2.1%)	15 (1.9%)	16 (3.3%)	2 (3.1%)	5 (2.0%)	2 (3.4%)	0	0
AEs leading to withdrawal[f]	28 (4.5%)	4 (3.4%)	353 (9.4%)	91 (11.4%)	47 (9.8%)	6 (9.2%)	19 (7.5%)	4 (6.8%)	14 (9.0%)	3 (10.7%)
AEs leading to dose reduction/ interruption[g]	21 (3.4%)	7 (6.0%)	568 (15.2%)	123 (15.4%)	102 (21.2%)	10 (15.4%)	26 (10.3%)	5 (8.5%)	4 (2.6%)	2 (7.1%)
Deaths[h,i]	1 (0.2%)	0	9 (0.2%)	6 (0.8%)	1 (0.2%)	0	1 (0.4%)	0	0	0

Data Source: ISS Table 6.2.1[a], ISS Table 7.2.1[c], ISS Table 7.6.1[d], ISS Table 7.10.1, ISS Table 8.2.1[g], ISS Table 9.2.1[g], ISS Listing 1[h]

Table includes data from all phases of Studies 2001, 2301 (DLP 10 NOV 2014), 3000, 3001, 3002, 3003, 3004, 3005, 3101, US01 and period 1 of 2328.
AE=adverse event; HAL=haloperidol; ILO Comb=combined iloperidone; RIS=risperidone; ZIP=ziprasidone
All adverse events are treatment emergent (TEAE).
[i]Includes only deaths that occurred in the 9 integrated studies.

Gender

Women have a 48% higher exposure for Iloperidone and the metabolites P88 and P95 compared to men. Significantly, more women had an AE that led to a dose reduction or interruption compared to men.

Safety profile by sex, Study Group 1 (safety population):

Total n (%) of patients with:	Placebo (N=737)		ILO Combined (N=4540)		HAL (N=546)		RIS (N=311)		ZIP (N=184)	
	M (N=481)	F (N=256)	M (N=2983)	F (N=1557)	M (N=347)	F (N=199)	M (N=214)	F (N=97)	M (N=138)	F (N=46)
Adverse Events[a]	329 (68.4%)	166 (64.8%)	2420 (81.1%)	1298 (83.4%)	315 (90.8%)	188 (94.5%)	168 (78.5%)	84 (86.6%)	119 (86.2%)	41 (89.1%)
Drug-related[b]	191 (39.7%)	85 (33.2%)	1616 (54.2%)	868 (55.7%)	251 (72.3%)	135 (67.8%)	98 (45.8%)	57 (58.8%)	107 (77.5%)	34 (73.9%)
Severe[c]	52 (10.8%)	29 (11.3%)	471 (15.8%)	273 (17.5%)	107 (30.8%)	57 (28.6%)	33 (15.4%)	14 (14.4%)	11 (8.0%)	4 (8.7%)
Serious AEs[d]	34 (7.1%)	19 (7.4%)	419 (14.0%)	269 (17.3%)	52 (15.0%)	36 (18.1%)	24 (11.2%)	8 (8.2%)	2 (1.4%)	0
Drug-related[e]	6 (1.2%)	5 (2.0%)	56 (1.9%)	39 (2.5%)	12 (3.5%)	6 (3.0%)	3 (1.4%)	4 (4.1%)	0	0
AEs leading to withdrawal[f]	20 (4.2%)	12 (4.7%)	295 (9.9%)	149 (9.6%)	28 (8.1%)	25 (12.6%)	17 (7.9%)	6 (6.2%)	12 (8.7%)	5 (10.9%)
AEs leading to dose reduction/ interruption[g]	12 (2.5%)	16 (6.3%)	395 (13.2%)	296 (19.0%)	70 (20.2%)	42 (21.1%)	24 (11.2%)	7 (7.2%)	4 (2.9%)	2 (4.3%)
Deaths[h,i]	0	1 (0.3%)	10 (0.3%)	5 (0.3%)	0	1 (0.5%)	0	1 (1.0%)	0	0

Data Source: ISS Table 6.3.1[a], ISS Table 7.3.1[c], ISS Table 7.7.1[d], ISS Table 7.11.1, ISS Table 8.3.1[g], ISS Table 9.3.1[g], ISS Listing 1[h]

Table includes data from all phases of Studies 2001, 2301 (DLP 10 NOV 2014), 3000, 3001, 3002, 3003, 3004, 3005, 3101, US01 and period 1 of Study 2328.

AE=adverse event; HAL=haloperidol; ILO=iloperidone; RIS=risperidone; ZIP=ziprasidone
All adverse events are treatment emergent (TEAE).
[i]Includes only deaths that occurred in the 9 integrated studies.

Race

Patients listed as Asians and "other" have significantly more serious adverse events than other races in the Iloperidone group. The same pattern is not apparent in the other treatment groups.

Safety profile by race, Study Group 1 (safety population):

Total n (%) of patients with:	Placebo (N=737)			ILO Comb. (N=4540)			HAL (N=546)			RIS (N=311)		
	W (N=383)	B (N=250)	A/O (N=59)	W (N=2345)	B (N=1172)	A/O (N=1023)	W (N=287)	B (N=71)	A/O (N=188)	W (N=210)	B (N=80)	A/O (N=21)
Adverse events[a]	252 (65.8%)	182 (72.8%)	28 (47.5%)	1957 (83.5%)	940 (80.2%)	821 (80.2%)	264 (92.0%)	69 (97.2%)	170 (90.4%)	166 (79.0%)	69 (86.3%)	17 (81.0%)
Drug-related[b]	132 (34.5%)	101 (40.4%)	43 (72.9%)	1299 (55.4%)	636 (54.3%)	548 (53.6%)	199 (69.3%)	48 (67.6%)	139 (73.9%)	104 (49.5%)	40 (50.0%)	11 (52.4%)
Severe[c]	47 (12.3%)	26 (10.4%)	8 (13.6%)	428 (18.3%)	122 (10.4%)	194 (30.3%)	88 (30.7%)	18 (25.4%)	58 (30.9%)	32 (15.2%)	13 (16.3%)	2 (9.5%)
Serious AEs[d]	29 (7.6%)	14 (5.6%)	10 (16.9%)	408 (17.4%)	111 (9.5%)	169 (26.4%)	45 (15.7%)	12 (16.9%)	31 (16.5%)	18 (8.6%)	12 (15.0%)	2 (9.5%)
Drug-related[e]	4 (1.0%)	3 (1.2%)	4 (6.8%)	52 (2.2%)	14 (1.2%)	29 (4.5%)	7 (2.4%)	3 (4.2%)	8 (4.3%)	3 (1.4%)	3 (3.8%)	1 (4.8%)
AEs leading to withdrawal[f]	12 (3.1%)	15 (6.0%)	5 (8.5%)	246 (10.5%)	114 (9.7%)	84 (8.2%)	30 (10.5%)	8 (11.3%)	15 (8.0%)	14 (6.7%)	6 (7.5%)	3 (14.3%)
AEs leading to dose reduction/ interruption[g]	19 (3.3%)	4 (1.6%)	5 (8.5%)	432 (18.4%)	92 (7.8%)	167 (16.3%)	68 (23.7%)	4 (5.6%)	40 (21.3%)	23 (11.0%)	7 (8.8%)	1 (4.8%)
Deaths[h,i]	0	1 (0.5%)	0	10 (0.4%)	2 (0.2%)	4 (0.4%)	0	0	1 (0.5%)	1 (0.5%)	0	0

Refer to footnotes on last page.
ZIP group shown on next page

(continued)

Total n (%) of patients with:	ZIP (N=184)		
	W (N=67)	B (N=93)	A/O (N=24)
Adverse events[a]	59 (88.1%)	82 (88.2%)	19 (79.2%)
Drug-related[b]	54 (80.6%)	71 (76.3%)	16 (66.7%)
Severe[c]	6 (9.0%)	7 (7.5%)	2 (8.3%)
Serious AEs[d]	0	2 (2.2%)	0
Drug-related[e]	0	0	0
AEs leading to withdrawal[f]	7 (10.4%)	9 (9.7%)	1 (4.2%)
AEs leading to dose reduction/ interruption[g]	1 (1.5%)	4 (4.3%)	1 (4.2%)
Deaths[h,i]	0	0	0

Data Source: ISS Table 6.4.1[a], ISS Table 7.4.1[c], ISS Table 7.8.1[d], ISS Table 7.12.1[e], ISS Table 8.4.1[b], ISS Table 9.4.1[g], ISS Listing 1[h]

Table includes data from all phases of Studies 2001, 2301 (DLP 10 NOV 2014), 3000, 3001, 3002, 3003, 3004, 3005, 3101, US01 and period 1 of Study 2328.

AE=adverse event; HAL=haloperidol; ILO Comb=combined iloperidone; RIS=risperidone; ZIP=ziprasidone

All adverse events are treatment emergent (TEAE).

"Asian" and "other" have been combined for the sake of space in the in-text table.

[i] Includes only deaths that occurred in the 9 integrated studies.

Safety related to drug-drug interactions and other interactions

Iloperidone and its metabolites, P88 and P95, do not induce CYP enzymes, but iloperidone and P88 may inhibit their activity.

Both CYP3A4 and CYP2D6 are responsible for Iloperidone metabolism. Inhibitors of CYP3A4 (e.g. ketoconazole) or CYP2D6 (e.g. fluoxetine, paroxetine) can inhibit Iloperidone elimination and cause

increased blood levels, increasing in turn the risk of exposure-related adverse events, including QT prolongation. The risk of the pharmacodynamic interaction with other QTc-prolonging medicines is a concern that the Applicant has not satisfactorily discussed.

Please refer to clinical pharmacology section.

Discontinuation due to adverse events

Adverse Events Leading to Dose Modification

For Study Group 1, adverse events led to dose modification (i.e., dose reduction or interruption) in 15.2% of Iloperidone-treated patients. This was higher compared to the placebo (3.8%) and ziprasidone (3.3%) groups, but similar to the haloperidol (20.5%) and risperidone (10.0%) groups.

Adverse Events Leading to Permanent Discontinuation of Study Drug

Overall, for Study Group 1, adverse events led to permanent discontinuation of treatment in 9.8% of patients in the combined Iloperidone group. This was similar to the incidence in the other comparator groups (7.4% to 9.7%). 11 patients discontinued due to QT prolongation and the frequency of discontinuation was dose related.

Permanent discontinuation of treatment due to Adverse Events in three or more Iloperidone-treated patients, Study Group 1 (safety population):

SOC Preferred Term	Placebo (N=737)	ILO 4-8 mg/d (N=1311)	ILO 10-16 mg/d (N=2384)	ILO 20-24 mg/d (N=845)	ILO Comb. (N=4540)	HAL 5-20 mg/d (N=546)	RIS 4-8 mg/d (N=311)	ZIP 160 mg/d (N=184)
N (%) of pts who dc'd due to TEAE	*32 (4.3%)*	*154 (11.7%)*	*220 (9.2%)*	*70 (8.3%)*	*444 (9.8%)*	*53 (9.7%)*	*23 (7.4%)*	*17 (9.2%)*
Cardiac disorders	**2 (0.3%)**	**15 (1.1%)**	**28 (1.2%)**	**3 (0.4%)**	**46 (1.0%)**	**1 (0.2%)**	**0**	**1 (0.5%)**
Tachycardia	0	6 (0.5%)	5 (0.2%)	1 (0.1%)	12 (0.3%)	1 (0.2%)	0	0
Palpitations	0	3 (0.2%)	8 (0.3%)	0	11 (0.2%)	0	0	0
Gastrointestinal disorders	**1 (0.1%)**	**12 (0.9%)**	**19 (0.8%)**	**3 (0.4%)**	**34 (0.7%)**	**1 (0.2%)**	**4 (1.3%)**	**1 (0.5%)**
Nausea	0	7 (0.5%)	9 (0.4%)	0	16 (0.4%)	1 (0.2%)	1 (0.3%)	0
Vomiting	1 (0.1%)	3 (0.2%)	4 (0.2%)	0	7 (0.2%)	0	0	0
General disorders and administration site conditions	**1 (0.1%)**	**10 (0.8%)**	**22 (0.9%)**	**1 (0.1%)**	**33 (0.7%)**	**2 (0.4%)**	**2 (0.6%)**	**0**
Asthenia	0	2 (0.2%)	8 (0.3%)	0	10 (0.2%)	0	0	0
Fatigue	0	4 (0.3%)	4 (0.2%)	0	8 (0.2%)	0	0	0
Oedema peripheral	0	1 (0.1%)	1 (0.0%)	1 (0.2%)	3 (0.1%)	0	1 (0.3%)	0
Infections and infestations	**0**	**2 (0.2%)**	**6 (0.3%)**	**1 (0.1%)**	**9 (0.2%)**	**1 (0.2%)**	**0**	**0**
Influenza	0	1 (0.1%)	2 (0.1%)	0	3 (0.1%)	0	0	0
Investigations	**1 (0.1%)**	**10 (0.8%)**	**21 (0.9%)**	**13 (1.5%)**	**44 (1.0%)**	**0**	**2 (0.6%)**	**2 (1.1%)**
Blood creatine phosphokinase increased	0	3 (0.2%)	3 (0.1)%	0	6 (0.1%)	0	1 (0.3%)	0
Electrocardiogram QT prolonged	0	1 (0.1%)	6 (0.3%)	4 (0.5%)	11 (0.2%)	0	0	0
Weight increased	0	1 (0.1%)	3 (0.1%)	2 (0.2%)	6 (0.1%)	0	0	0
Hepatic enzyme increased	0	1 (0.1%)	1 (0.1%)	1 (0.1%)	3 (0.1%)	0	0	0

SOC Preferred Term	Placebo (N=737)	ILO 4-8 mg/d (N=1311)	ILO 10-16 mg/d (N=2384)	ILO 20-24 mg/d (N=845)	ILO Comb. (N=4540)	HAL 5-20 mg/d (N=546)	RIS 4-8 mg/d (N=311)	ZIP 160 mg/d (N=184)
Nervous system disorders	**6 (0.8%)**	**35 (2.7%)**	**51 (2.1%)**	**10 (1.2%)**	**96 (2.1%)**	**33 (6.0%)**	**10 (3.2%)**	**7 (3.8%)**
Dizziness	2 (0.3%)	7 (0.5%)	24 (1.0%)	2 (0.2%)	33 (0.7%)	0	3 (1.0%)	0
Headache	0	2 (0.2%)	9 (0.4%)	1 (0.1%)	12 (0.3%)	0	1 (0.3%)	2 (1.1%)
Syncope	0	3 (0.2%)	2 (0.1%)	2 (0.2%)	7 (0.2%)	1 (0.2%)	1 (0.3%)	0
Tremor	0	5 (0.4%)	0	0	5 (0.1%)	8 (1.5%)	1 (0.3%)	0
Sedation	0	3 (0.2%)	4 (0.2%)	1 (0.1%)	8 (0.2%)	1 (0.2%)	0	1 (0.5%)
Somnolence	0	1 (0.1%)	5 (0.2%)	2 (0.2%)	8 (0.2%)	0	2 (0.6%)	1 (0.5%)
Akathisia	1 (0.1%)	4 (0.3%)	1 (0.1%)	0	5 (0.1%)	11 (2.0%)	0	2 (1.1%)
Convulsion	2 (0.3%)	2 (0.2%)	1 (0.1%)	1 (0.1%)	4 (0.1%)	0	0	0
Generalized Tonic-Clonic Seizure	0	2 (0.2%)	1 (0.1%)	0	3 (0.1%)	0	0	0
Psychiatric disorders	**15 (2.0%)**	**46 (3.5%)**	**72 (3.0%)**	**26 (3.1%)**	**144 (3.2%)**	**12 (2.2%)**	**6 (1.9%)**	**8 (4.3%)**
Psychotic disorder	5 (0.7%)	6 (0.5%)	13 (0.5%)	6 (0.7%)	25 (0.6%)	3 (0.5%)	1 (0.3%)	4 (2.2%)
Suicidal ideation	1 (0.1%)	3 (0.2%)	7 (0.3%)	2 (0.2%)	12 (0.3%)	3 (0.5%)	1 (0.3%)	0
Schizophrenia	2 (0.3%)	7 (0.5%)	21 (0.9%)	9 (1.1%)	37 (0.8%)	0	1 (0.3%)	0
Depression	0	2 (0.2%)	7 (0.3%)	1 (0.1%)	10 (0.2%)	0	0	1 (0.5%)
Suicide attempt	0	6 (0.5%)	1 (0.0%)	1 (0.1%)	8 (0.2%)	1 (0.2%)	1 (0.3%)	0
Anxiety	0	2 (0.2%)	6 (0.3%)	0	8 (0.2%)	0	0	2 (1.1%)
Agitation	1 (0.1%)	3 (0.2%)	3 (0.1%)	2 (0.2%)	8 (0.2%)	2 (0.4%)	0	1 (0.5%)
Completed suicide	0	2 (0.2%)	1 (0.0%)	0	3 (0.1%)	1 (0.2%)	0	0
Confusional state	0	3 (0.2%)	0	0	4 (0.1%)	0	0	0
Delusion	0	1 (0.1%)	1 (0.0%)	0	2 (0.0%)	0	0	0
Insomnia	2 (0.3%)	2 (0.2%)	1 (0.0%)	1 (0.1%)	9 (0.2%)	3 (0.5%)	1 (0.3%)	0
Mania	0	1 (0.1%)	2 (0.1%)	0	3 (0.1%)	0	0	0
Renal and urinary disorders	**0**	**4 (0.3%)**	**2 (0.1%)**	**3 (0.4%)**	**9 (0.2%)**	**1 (0.2%)**	**0**	**0**
Urinary incontinence	0	2 (0.2%)	1 (0.0%)	1 (0.1%)	4 (0.1%)	0	0	0
Reproductive & breast disorders	**1 (0.1%)**	**11 (0.8%)**	**14 (0.6%)**	**6 (0.7%)**	**31 (0.7%)**	**0**	**3 (1.0%)**	**0**
Erectile dysfunction	0	4 (0.3%)	2 (0.1%)	1 (0.1%)	7 (0.2%)	0	1 (0.3%)	0
Ejaculation failure	0	2 (0.2%)	3 (0.1%)	0	5 (0.1%)	0	1 (0.3%)	0

SOC Preferred Term	Placebo (N=737)	ILO 4-8 mg/d (N=1311)	ILO 10-16 mg/d (N=2384)	ILO 20-24 mg/d (N=845)	ILO Comb. (N=4540)	HAL 5-20 mg/d (N=546)	RIS 4-8 mg/d (N=311)	ZIP 160 mg/d (N=184)
Respiratory, thoracic and mediastinal disorders	**0**	**9 (0.7%)**	**13 (0.5%)**	**2 (0.2%)**	**24 (0.5%)**	**0**	**0**	**0**
Dyspnoea	0	3 (0.2%)	4 (0.2%)	1 (0.1%)	8 (0.2%)	0	0	0
Skin and subcutaneous tissue disorders	**1 (0.1%)**	**7 (0.5%)**	**3 (0.1%)**	**0**	**10 (0.2%)**	**1 (0.2%)**	**0**	**0**
Rash	1 (0.1%)	3 (0.2%)	1 (0.0%)	0	4 (0.1%)	0	0	0
Vascular disorders	**0**	**10 (0.8%)**	**11 (0.5%)**	**3 (0.4%)**	**24 (0.5%)**	**2 (0.4%)**	**0**	**0**
Orthostatic hypotension	0	5 (0.4%)	5 (0.2%)	1 (0.1%)	11 (0.2%)	1 (0.2%)	0	0
Hypotension	0	2 (0.2%)	5 (0.2%)	1 (0.1%)	8 (0.2%)	0	0	0
Hypertension	0	3 (0.2%)	1 (0.0%)	1 (0.1%)	5 (0.1%)	1 (0.2%)	0	0

Data Source: ISS Table 9.1.1

Table includes data from all phases of Studies 2001, 2301 (DLP 10 NOV 2014), 3000, 3001, 3002, 3003, 3004, 3005, 3101, US01 and period 1 of 2328.

Comb=combined; dc=discontinue; HAL=haloperidol; ILO=iloperidone; Pt=number of patients, RIS=risperidone; TEAE=treatment-emergent adverse event; ZIP=ziprasidone.

Patients who experienced multiple AEs within the same SOC were counted only once for that same SOC.

Patients who experienced the same AE multiple times within the same SOC were counted only once for the corresponding Preferred Term based on the highest degree of relationship.

Adverse events are sorted alphabetically by SOC and within each SOC the preferred term is presented by decreasing order of frequency in the combined iloperidone group.

Percentages are based on the total number of patients within each treatment/dose group.

Post marketing experience

Iloperidone was approved by the U.S. FDA in May 2009 and was commercially launched for sale in the U.S. by Novartis Pharmaceuticals in January 2010. The Applicant estimates an exposure of around 71,000 patients-years.

From the Vanda global US post-marketing surveillance database through 24 August 2016 there were 33 deaths in total. 3 patients died during sleep, 6 were sudden deaths, 6 cases were of cardiac origin. The rest were suicides (6), unknown (7), 2 of died of other reasons and 3 died due to pulmonary embolism.

2.6.1. Discussion on clinical safety

A total of 40 clinical studies have been conducted with Iloperidone. The integrated safety database includes 5530 adult patients with schizophrenia in 11 controlled clinical studies of which 4423 patients were exposed to Iloperidone during at least one phase of the studies. This means that 29 Phase 1 and 2 studies have not been integrated of which at least 5 studies in patients with schizophrenia treated with doses in accordance with the proposed posology. There was overall no difference with regards to adverse events from these studies as compared to the pooled studies.

Many of the studies included patients with schizophrenia and schizoaffective disease. There does not appear to be a difference in the AE profile in the two patient groups. In the double blinded placebo controlled trials, the demographics were balanced with regards to prior hospitalisation. The proposed maximum dose is 12 mg twice daily (24 mg/day). Exposure for more than 12 months with this dose amount to 265 patient-years for the 20-24 mg dose in the clinical trials. There are additional post-marketing data with this dose from more than 10,000 patient-years. With the post-marketing data there is a sufficiently large safety database for the 20-24 mg dose.

Only 28 patients 65 years or older have been included the integrated clinical studies. The safety in patients 65 years or older has thus not been sufficiently established. Thus, the use in the elderly cannot be considered, especially taking into account that Iloperidone causes QT prolongation and hypotension, including orthostatic hypotension. These adverse events are expected to be more pronounced in the elderly.

Women have a 48% higher exposure of Iloperidone and the metabolites P88 and P95 compared to men and more women had an AE that led to a dose reduction or interruption. Data from the double blind placebo controlled trials do not indicate that women are more likely to experience adverse event as compared to men. Approximately 10% discontinued Iloperidone due to a treatment emergent adverse events, and this was comparable to the other active treatments indicating that, overall, Iloperidone is not better or worse tolerated than haloperidol, risperidone or ziprasidone.

Although, the safety and tolerability profile of Iloperidone is largely similar to that of the other two 2nd generation antipsychotics, risperidone and ziprasidone, there are important differences in the incidence and as regards to the cardiac concern. Indeed, the incidence of serious adverse events were considerable higher (15.2%) in the Iloperidone group compared to the ziprasidone group (1.1%) and risperidone group (10.3%) but similar to haloperidol.

In addition, the main issue with Iloperidone is its cardiac safety profile and in particular to the fact that it causes clinically relevant QTcF prolongation. Preclinical studies have demonstrated that Iloperidone has the ability to cause QTc prolongation, and this has been confirmed in the thorough QTc study as well as in the Phase 3 clinical programme. The QTcF prolongation of Iloperidone 8 mg b.i.d. and 12 mg b.i.d. was similar to that of ziprasidone 80 mg b.i.d. approximately 9 msec. However, with full metabolic CYP

inhibition the mean QTc was 19.3 msec whereas with full CYP inhibition of ziprasidone (CYP3A4 inhibition) it is 15.9 msec.

Furthermore, an increase of more than 60 msec from baseline when treating with a medicine is a concern and would usually lead to discontinuation, as this is associated with an increased risk of arrhythmia. It is noted that two patients (3%) in the Iloperidone group developed a QTcF of more than 60 msec in the 8 mg-12 mg b.i.d. groups without metabolic inhibition and with maximum metabolic inhibition 3 (10%) patients in the 12 mg b.i.d. group and 1 patient in the 8 mg bid group had a QTcF of more than 60 msec. Some patients presented symptomatic events associated with the QTc prolongations: one patient developed palpitation in a setting of a bradycardia, hypotension then "presyncope" associated with QTc increase ≥ 60ms. For 10 other cases, the clinical events reported together with QTc prolongation were tachycardia (6), hypotension (2) and/or bradycardia (2).

None in the ziprasidone developed QTcF of more than 60 msec regardless of metabolic inhibition.

Looking at the clinical safety data, Safety group 1, 4.5% of the patients treated with Iloperidone regardless of dose (4-24 mg/day) had an increase om more than 60 msec at some time point during the clinical studies. In the ziprasidone group (160 mg/day) it was 1.6%.

3 patients had at some time-point a QTcF of more than 500 msec (Iloperidone 10-16 mg/day group). This was not seen in the ziprasidone group although fewer patients were exposed to ziprasidone.

Furthermore, Iloperidone and ziprasidone bear a different arrhythmogenic potential. The hERG IC50 values of 29-37 nM for Iloperidone and 56 nM for P88. For ziprasidone hERG IC50 value was 55 nM. APIs showing a ratio of hERG IC50 and unbound maximum plasma concentration of less than 30 have a high propensity to elicit Torsade de Point arrhythmia (Redfern et al, 2003). The respective ratio of hERG IC50/free Cmax amount to 8.4-59 for Iloperidone (considering a protein binding of 93-99%, reported in different studies in the Applicant´s dossier) and 134.5 for ziprasidone (protein binding of 99.9% as described in approval reviews for ziprasidone).

There was a clear dose dependent increase in QTcF, and when the two major metabolic pathways for Iloperidone CYP2D6 and CYP3A4 were inhibited, the QTcF increased further. Concomitant use of strong inhibitors of CYP2D6 and CYP3A4 is thus inadvisable. Furthermore, QTc evaluation of patients who are CYP2D6 poor metabolizers showed significantly increased QTc prolongation compared to patients with the wild type genotype. As outlined by the ad hoc group, the amount of evidence available for homozygotes does not allow to establish a safe dose in this population. This suggests that genotyping prior to initiating Iloperidone treatment at any dose should be done. However, this may not feasible as stated by the ad hoc expert group. It could also be considered that for patients who are poor CYP2D6 metabolizers, the concomitant use of CYP3A4 strong inhibitors is not advisable. It is unknown what the risks associated with the administration of Iloperidone in patients with unknown CYP2D6*4 and *10 genotype profiles would be given that those patients could be exposed to higher doses than the maximum recommended (12mg/day). Furthermore, it is unknown what the effect of weak and moderate inhibitors of CYP2D6 and/or CYP3A4 will have on the QTc.

The point estimate of the overall mortality rate per 100 patient-years is not higher in the Iloperidone group compared to placebo or risperidone. However, lower exposure in the latter two groups make the precise estimation of the rate of a rare event difficult. More deaths occurred in the Iloperidone group than in any of the other groups and 6 of the deaths might be linked to QT prolongation (arrhythmia, sudden cardiac arrest and sudden death). Considering 4423 patients have in the clinical trial program been exposed to Iloperidone, 0.14% of all treated patients died due to sudden death or death due to cardiac AE. This equates to a number needed to harm of 714. Or to put it differently for every 714 patients treated with Iloperidone, one will die of a sudden death or a cardiac death.

In addition, from the Vanda global US post-marketing surveillance database through 24 August 2016 there were 33 deaths in total. 3 patients died during sleep, 6 were sudden deaths, 6 cases were of cardiac origin. The rest were suicides (6), unknown (7), 2 of died of other reasons and 3 died due to pulmonary embolism. Moreover, in several cases where cause of death was not reported or unknown a cardiac origin could. Concerning the post-marketing experience, it is difficult to conclude on the calculation made by the Applicant on the excess mortality. This is due to difficulties in evaluating the matching and the assumed under-reporting rate. From the qualitative point of view, in the opinion of the assessor, and considering the age of the patient, time since initiation of treatment, and circumstances of the deaths, 15 cases can possibly be considered very likely associated with Iloperidone. At least one fatal case could possibly have been preceded by ventricular arrhythmia and torsade de pointes.

The Applicant has not addressed whether there have been literature reports of arrhythmia. In fact at least one a case report describe a 29-year old man who experienced ventricular premature contraction while receiving 16 mg/day Iloperidone (Achalia R. and Andrade C, Indian journal of psychiatry, 2013).

The CYP2D6 genotype was not known in any of cases of death in clinical trials or post-marketing.

Overall, there is evidence both from the clinical trial data as well as post-marketing experience that the use of Iloperidone is associated with an increased risk of sudden or cardiac related death.

The ad hoc experts' group was also consulted on issues related to safety (see below) confirmed the existence of an arrhythmogenic potential of Iloperidone, also noting that the magnitude of the corresponding risk of clinically relevant events cannot be fully assessed with the currently available data.

As alluded to by the ad hoc expert group, the emphasis on CYP2D6 genotyping could provide a false reassurance to patients who do not carry the mutations and to their physicians. The experts expressed the view that sequential ECGs should be done as they would provide a more reliable indicator of the risk of arrhythmia. This should be done at baseline, during titration to the target dose and thereafter at any dose increase, but also when other medications with effect on QT prolongation or interfering with the pharmacokinetics of Iloperidone are added. Additional periodic ECG evaluations would need to take into consideration a balance between the risks connected to a delayed-appearance of QT prolongation and feasibility and sustainability issues. Considering that many patients with schizophrenia are treated in an ambulatory setting, even in private practice, the extent of ECG monitoring plus the recommendation for the availability of a cardiologist to support the interpretation of the ECG examinations (as advised by the ad-hoc expert group), it is at best uncertain if these risk mitigation strategies will be feasible throughout Europe in all treatment settings and centers. Furthermore, it will be difficult to capture any late occurrence of QTc prolongation. In fact, one patient in the clinical development programme had a QTc of more than 500 msec, which occurred more than 3 months after initiation of treatment.

In the Phase 3 clinical programme, the outlier analysis revealed that, regardless of dose (4-8 mg/day or 10-16 mg/day Iloperidone), approximately 5% had a ≥ 60 msec. increase in QTcF at some point during treatment. An increase in QTcF of more than 60 msec. from baseline is considered proarrhythmic. In addition, 3.2% of the patients had a QTc ≥450 ms at some time point during the clinical trial programme. Furthermore, Iloperidone causes an increase in mean heart rate from baseline ranging from -2.4-5.1 bpm (worst possible value). This is comparable to the increase in heart rate observed in the risperidone (5.4 bpm) and ziprasidone groups (1.6 bpm). However, Iloperidone regardless of dose, is more likely to cause tachycardia (HR ≥120 bpm) or an increase of 15 bpm from baseline compared to the other treatment groups. An increase in heart rate has for other medicines been associated with an increase in major adverse cardiac events (MACE). Data from the clinical trials do not indicate that there is an increased risk, but most patients have only been exposed in short term studies and sufficiently powered long term safety data would be needed to estimate if there is indeed an increased risk. In addition, the increase in pulse

rate seems to return to baseline after approximately one month of treatment. The increased pulse rate could be caused by hypotension, which occurred in approximately 25% of the patients.

Cardiac adverse events occurred more frequently in the Iloperidone combined group and the ziprasidone group compared to the other treatment groups. However, more patients discontinued, had a dose reduction/interruption or died due to a cardiac adverse event in the Iloperidone group compared to the ziprasidone group. This could suggest that Iloperidone has a more adverse cardiac safety profile than ziprasidone.

With regard to metabolic adverse events, there is no doubt that Iloperidone causes significant weight increase (more than 30% had a ≥7% increase in weight) and the frequency was higher compared to the other treatment groups (placebo 9.2%, haloperidol 25.9%, risperidone 21.1% and ziprasidone 7.2%). The mean maximum weight increase in Iloperidone-treated patients was approximately 5.25 kg based on clinical trials data. Most of the weight gain is seen with in the first 6 weeks of treatment and stabilizes at around 4 months of treatment. In several post-marketing cases for which information on the range of weight gain is available, the observed weight gain appeared to be more significant (>5 kg) and occurred often after short-term treatment duration. It is not clear if the weight gain was a consequence of oedema (oedema was frequently reported post-marketing) or of a metabolic origin. Patients with heart failure may experience rapid changes in weight caused by fluid retention. However, in the clinical trial there was no difference between placebo and Iloperidone groups regarding the risk of oedema.

The incidence of hyperglycaemia was higher in the Iloperidone group than in placebo and the incidence increased with increased exposure and duration of treatment. It seems that an excess of approximately 4-5% of the patients develop type 2 diabetes when treated with Iloperidone compared to placebo or ziprasidone. It is not known if the development of hyperglycaemia is correlated to a significant weight increase. Furthermore, it is noted that one patient died due to uncontrollable diabetes. Iloperidone only seems to cause slight dyslipidaemia as compared to placebo.

Iloperidone can cause elevated prolactin levels but not as frequently as haloperidol and risperidone. The percentages of patients who had a normal prolactin value at baseline and an elevated prolactin value during treatment are as follows: 4.8%, 16.9%, 71.8%, 91.2% and 10.3% for the placebo, combined Iloperidone, haloperidol, risperidone and ziprasidone groups, respectively.

Other laboratory values showed that few patients in each Iloperidone treatment group had a shift from Grade 0 to Grade 3 or Grade 4 lymphocytopenia or neutropenia. This was similar to the placebo group. Additionally, it is noted that slightly more patients had hepatic transaminase increases in the Iloperidone group than the placebo group. Even if the grade shifts analysis were comparable to placebo, three patients discontinued due to elevated hepatic transaminase enzymes indicating that, although rarely Iloperidone, may cause clinically relevant increase in hepatic transaminases.

Hypothermia is described as a potential adverse reaction of antipsychotic drug use due to their alteration on thermoregulatory processes in the human body as supported notably by several publications and two cases have been reported post-marketing.

In clinical trials, two deaths were caused by pylorus occlusion or volvulus and one case of serious colitis ischaemia. Gastrointestinal hypomotility and other gastrointestinal pertubations can be caused by antipsychotics and may induce intestinal necrosis. The causal link between Iloperidone and ischemic colitis or intestinal obstruction cannot be totally excluded.

Extrapyramidal symptoms (EPS) occurred less frequently in the Iloperidone group compared to the active treatment groups but occurred more frequently compared to placebo. The Extrapyramidal Symptoms Rating Scale (ESRS) showed a similar rating score in the Iloperidone, risperidone and ziprasidone groups. From the Barnes Akathisia Scale (BAS), regardless of BAS parameter, it is apparent that Iloperidone does

cause slightly more akathisia compared to placebo, but less compared to ziprasidone and risperidone and significantly less than haloperidol.

Sedation was dose related in the Iloperidone group and occurred most frequently in the ziprasidone group (23.9%) and in approximately 5% in the risperidone and Iloperidone groups and much less in the haloperidol group (1.8%) and placebo group (2.9%). The same pattern was not evident for the adverse event, somnolence (Iloperidone comb. 6.3%, haloperidol 6.6%, risperidone 6.1%, ziprasidone 7.6% and placebo 1.9%).

Schizophrenia-related adverse events are strongly linked to an unsatisfactory therapeutic effect and a lack of efficacy of treatment conducted to a potential exacerbation of schizophrenia. Psychotic disorder was a common adverse event among Iloperidone-treated patients (6.2%). Among the 3 Iloperidone dose groups, the highest incidence of schizophrenia-related adverse events occurred in the ILO 4-8 mg/day group (36.7%), followed by the ILO 10-16 mg/day group (33.7%) and last by the ILO 20-24 mg/day group (16.8%), which was lower than the placebo rate (25.8%). These data support a higher clinical effect at the maximal suggested dose of Iloperidone 24mg/d. It is a concern that psychotic disorders may reflect lack of efficacy of the treatment, in particular at the lowest Iloperidone doses (4-8 mg/day and 10-16 mg/day).

Despite the possibility of a suicide attempt is inherent in psychotic illness, the risk of suicidality was not systematically explored for Iloperidone in all clinical trials. Given the insufficient analysis provided by the Applicant, no link between suicidal events and the phase of treatment (titration vs stabilization phase vs relapse prevention phase) could be analysed. Suicidality is considered a safety concern and an important potential risk.

Additional expert consultations

The CHMP has sought the advice of an expert group also on the following issues related to safety:

1) What is the expert group´s view on

a the evidence of a pronounced arrhythmogenic potential of iloperidone (taking into account preclinical and clinical data)?

b the proposed CYP2D6 genotyping and its applicability in common clinical practice?

c whether the CYP2D6 genotyping should be done prior to initiating treatment?

2) In the view of the expert group´s, are there other viable options for the safe clinical use of iloperidone, in case genotyping is not feasible or available?

3) Does the expert group´s consider the proposed dose reduction strategy for minimizing cardiac risk is sufficiently supported by available data?

The ad-hoc experts group meeting was held on 5 May 2017.

The Company presented their view in writing and at the meeting.

The answers from the experts are shown below:

1a. What is the experts' view on the evidence of a pronounced arrhythmogenic potential of Iloperidone (taking into account preclinical and clinical data)?

The experts concurred on the existence of an arrhythmogenic potential of Iloperidone. The magnitude of the corresponding risk of clinically relevant events cannot be fully assessed with the currently available data.

1b. What is the experts' view on the proposed CYP2D6 genotyping and its applicability in common clinical practice?

The experts expressed the view that CYP2D6 genotyping might not be feasible in all contexts – as the availability of the test might vary and also in consideration of its cost[1] and of the delay that it would impose on starting the treatment with Iloperidone.

1c. What is the experts' view on whether the CYP2D6 genotyping should be done prior to initiating treatment?

The experts agreed that the CYP2D6 should not be considered mandatory prior to initiating treatment, but that it might be useful – when feasible – in order to identify and potentially exclude from the treatment patients that are homozygotes for the *4 or for the *10 mutation.

The experts also questioned the validity of any conclusion on the cardiac safety of the use of Iloperidone solely made on the basis of the genotype for CYP2D6, as this – concurring to determine the extent of exposure – is only one of many elements of the causal chain of the relationship between administration of Iloperidone and risk of QT prolongation – known and unknown variants of susceptibility also being relevant. Additional risk factors for cardiac events in general - of high prevalence in subjects with schizophrenia - have also been discussed.

The emphasis on CYP2D6 genotyping could provide a false reassurance to patients who do not carry the mutations and to their physicians and therefore should not be considered a substitute for phenotyping. This is also in consideration of the lack of information on the genotype of the cases of sudden death.

2. In the view of the SAG, are there other viable options for the safe clinical use of Iloperidone, in case genotyping is not feasible or available?

The experts expressed the view that sequential ECGs should be done as they would provide a more reliable indicator of the risk of arrhythmia. This should be done at baseline, during titration to the target dose and thereafter at any dose increase, but also when other medications with effect on QT prolongation or interfering with the pharmacokinetics of Iloperidone are added.

The frequency of additional periodic ECG evaluations would need to take into consideration a balance between the risks connected to a delayed-appearance of QT prolongation and feasibility and sustainability issues.

3. Do the experts consider the proposed dose reduction strategy for minimizing cardiac risk is sufficiently supported by available data?

The experts expressed the view that the effectiveness of the proposed dose reduction strategy is not supported by the amount of currently available evidence in the patients who are homozygotes for the *4 or for the *10 mutation.

The experts also asserted that such a strategy might not be needed in the heterozygotes.

2.6.2. Conclusions on the clinical safety

Iloperidone has a substantial arrhythmogenic potential, as it can be concluded based on all available non-clinical and clinical data (including the thorough QTc study, the overall clinical program and also the cases of cardiac-related/sudden unexplained death in clinical trials and post-marketing). Furthermore,

[1] This aspect has been mentioned - with reference to potential varying degrees of concern between different Member States - by the experts while addressing feasibility of genotyping. Costs and other economic considerations do not however inform the CHMP decision on the benefit/risk of a medicinal product.

due to the dose-dependent risk of QT prolongation and the metabolism of Iloperidone via CYP2D6, there is an increased risk of QT prolongation in patients who are CYP2D6 poor metabolisers.

CYP2D6 genotyping as well as extensive ECG monitoring is not considered feasible in all clinical settings nor will this be sufficient to minimize the risk.

Iloperidone was associated with extrapyramidal effects, but to a modest degree. Akathisia was reported by 4.0% of patients on iloperidone compared to 2.2% in patients receiving placebo.

In summary, the safety of Iloperidone has not been sufficiently demonstrated.

2.7. Risk Management Plan

The CHMP and the PRAC, having considered the data submitted, are of the opinion that, due to the concerns identified with this application, the RMP for Iloperidone is not acceptable at this stage.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. New Active Substance

The applicant compared the structure of iloperidone with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, in light of the negative recommendation, is of the opinion that it is not appropriate to conclude on the new active substance status at this time.

2.10. Product information

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling and package leaflet cannot be agreed at this stage.

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.* However, due to the aforementioned concerns a satisfactory package leaflet cannot be agreed at this stage.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Schizophrenia is a psychiatric disorder that affects approximately 1% of the world-wide and the EU population. It is characterized by the presence of positive symptoms (such as hallucinations and delusions) and negative symptoms (e.g. apathy, blunted affect and social withdrawal), as well as impairment of cognitive functions and mood symptoms. The disease is chronic and significantly debilitating on both the social and occupational functioning of patients. The disease is also associated with an increased mortality. More than 10% of patients with schizophrenia complete suicide in their lifetime. In addition, lifestyle factors (smoking, substance abuse, unhealthy food) contribute to the increased mortality.

3.1.2. Available therapies and unmet medical need

Medicines in use for the treatment of Schizophrenia are usually classified into first generation (or typical) and second-generation (or atypical) antipsychotics.

First-generation (or typical) antipsychotics such as chlorpromazine and haloperidol, reduce positive symptoms of psychosis by acting as antagonists on the D2 receptors of the mesolimbic pathway. The same effect on D2 receptors on the nigrostriatal pathway is believed to be associated with the high incidence of Extrapyramidal symptoms observed with these drugs. An upregulation of the same receptors on this pathway is believed to be the cause of the long-term development of tardive dyskinesia.

The class of second-generation (or atypical) antipsychotics includes clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, asenapine, lurasidone and sertindole. The medicines in this class share the characteristic of binding both the dopamine and serotonin receptors, but they are also different in the combination of receptors they bind and their affinity for those receptors. These differences result in differences in efficacy and in different safety profiles. Iloperidone is considered an atypical antipsychotic.

Typical antipsychotics or 1st generation antipsychotics include flupentixole, haloperidol, pimozid, luxpaine, periciazine, perphenazine, prochlorperazine, chlorprothixen, levomepromazine, melperone, pipamperone and sulpiride.

While significant advances have been made over the last fifty years, the pharmacological treatments available are merely symptomatic and mainly target the positive symptoms. A significant unmet medical need remains.

3.1.3. Main clinical studies

Study Phase and Sponsor	Study Number	Number of Subjects Exposed to Study Drug	
		All Treatments (including placebo and active controls)	Treated with Iloperidone
Phase III Novartis	ILP3000	610	393
	ILP3001	597	452
	ILP3002	553	417
	ILP3003	484	362
	ILP3004	613	367
	ILP3005	689	378
Phase III Vanda	VP-VYV-683-3101	597	300
Phase IIIb Novartis	ILO522D2301	635	635

Study 3101. A Randomized, Double-Blind, Placebo- and Ziprasidone-Controlled, Multicenter Study to Evaluate the Efficacy, Safety and Tolerability of a 24 mg/day Dose Iloperidone Given b.i.d.for 28 Days to Schizophrenic Patients in Acute Exacerbation Followed by a Long-Term Treatment Phase.

Study 3004.: A randomized, double-blind, placebo- and risperidone-controlled, multicenter study to evaluate the efficacy and safety of two non-overlapping dose ranges of iloperidone given b.i.d. for 42 days to schizophrenic patients and schizoaffective patients with acute or subacute exacerbation, followed by a risperidone controlled, long-term treatment phase with iloperidone given q.d.

Study 3000: A prospective, randomized, double-blind, placebo- and active-controlled, multicenter study to evaluate the efficacy and safety of three fixed doses of iloperidone (4, 8, and 12 mg/d) given b.i.d. for 42 days to schizophrenic patients and schizoaffective patients with acute or subacute exacerbation, followed by a double blind, active-controlled (haloperidol), flexible-dose, long-term, 20-week phase with iloperidone (4, 8, 12, or 16 mg/d) given q.d.

Clinical study 3005. A randomized, double-blind, placebo- and risperidone controlled, multicenter study to evaluate the efficacy and safety of two non-overlapping dose ranges of iloperidone given bid for 42 days to schizophrenic patients and schizoaffective patients followed by long-term treatment phase with iloperidone given q.d.

Clinical studies 3001, 3002 and 3003. Titles of studies were the same for each study: A prospective, randomized, multi-center, double-blind, flexible-dose, parallel-group study to determine the antipsychotic effect of iloperidone (dose range of 4-16 mg/day, given bid) as compared with haloperidol (dose range 5-20 mg/day, given bid) and to determine the safety of iloperidone in schizophrenic patients and schizoaffective patients.

Long-term efficacy

Study 2301. A multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate prevention of relapse in patients with schizophrenia receiving either flexible dose iloperidone or placebo in long-term use (up to 26 weeks) followed by up to 52 weeks of open-label extension Phase.

3.2. Favourable effects

Iloperidone has shown a modest efficacy in the short term treatment of schizophrenia. This effect has a delayed onset, which is a drawback in this setting.

In the pivotal short-term Study 3101 investigating patients with acute exacerbations of schizophrenia, Iloperidone resulted in a treatment difference on the PANSS Total score of around 5 points (95% CI -8.47 to -1.38). The same treatment difference was achieved with ziprasidone. Changes in favour of Iloperidone vs placebo were also observed with other scales and subscales addressing symptoms of schizophrenia (BPRS, PANSS Positive and Negative Symptoms scales and others) as well as assessment tools measuring global function.

Other short term-studies showed numerical changes favouring Iloperidone over placebo, but failed to show statistically significant changes, and Iloperidone was inferior to haloperidol 15 mg/day and risperidone 4-8 mg/day.

Long-term efficacy (maintenance of effect) in patients stabilised on Iloperidone was primarily documented in the randomised withdrawal study 2301. In the patients who continued on Iloperidone after the 14-24 week stabilisation phase, the average time to relapse or impending relapse was 140 days compared to 95 days in the subjects who were switched to placebo. The rate of relapse or impending relapse was 17.9% and 64.0%, respectively.

3.3. Uncertainties and limitations about favourable effects

In the trials submitted for review, Iloperidone inconsistently met the primary efficacy endpoint in prespecified analyses. Furthermore, the onset of action of Iloperidone was slower than for the other antipsychotics included in the clinical trials. In most studies, at least 3 weeks appeared to be required for full onset of action.

Doses as low as 4-8 mg/day appear to be effective in one study (3004), and in some studies doses of 12 mg/day (3000), 10-16 mg/day (3004) or 12-16 mg/day (3005) showed superiority to placebo. However, studies 3000 and 3005 were negative studies, and no correction for multiplicity was performed when evaluating 'superiority' of individual doses. Thus, there is no robust support for any statements concerning dose-response relationship below 24 mg/day (the dose used in study 3101). Thus, doses below 24 mg/day have not consistently shown to be effective.

In the trials where it has been compared to Haloperidol and Risperidone, Iloperidone seems to have a numerically smaller effect. This is especially true if the estimation takes into account all randomised patients, including the ones that discontinue early due to lack of efficacy. Particularly as there are no baseline predictors of early dropouts, this appears to be the necessary approach in estimating the effect on a population level.

The ability of Iloperidone to prevent relapses in patients stabilised on the same drug has been shown in a randomised withdrawal study. However, the trial does not directly inform on the ability of Iloperidone to prevent relapses in patients stabilised on other treatments.

3.4. Unfavourable effects

Iloperidone has a substantial arrhythmogenic potential, as it it can be concluded based on all available non-clinical and clinical data (including the thorough QTc study, the overall clinical program and also the cases of cardiac-related/sudden unexplained death in clinical trials and post-marketing).

In the thorough QTc study, the mean change in QTcF from baseline to steady state at Tmax was 15.4 msec in the group receiving Iloperidone 24 mg q.d. compared to 1.3 msec in the group receiving quetiapine (negative control). With full metabolic CYP inhibition the mean QTc was 19.3 msec.

Two patients (3%) in the Iloperidone group developed a QTcF of more than 60 msec in the 8 mg-12 mg b.i.d. groups without metabolic inhibition, and with maximum metabolic inhibition 3 (10%) patients in the 12 mg b.i.d. group and 1 patient in the 8 mg bid group had a QTcF of more than 60 msec. Some patients presented symptomatic events associated with the QTc prolongations: one patient developed palpitation in a setting of a bradycardia, hypotension then "presyncope" associated with QTc increase ≥ 60ms. For 10 other cases, the clinical events reported together with QTc prolongation were tachycardia (6), hypotension (2) and/or bradycardia (2).

In the Phase 3 studies, the proportion of patients with QTcF values ≥ 450 ms as well as the proportion of patients with large increase in QTcF (more than 60 msec) were clearly higher in the Iloperidone group than in the placebo group and looking at the double blinded placebo controlled part of the pooled safety results (safety group 2) QT prolongation occurred at similar frequency in the Iloperidone 10-16 mg groups as compared to Ziprasidone. In Study Group 1, 4.5% of the patients treated with Iloperidone regardless of dose (4-24 mg/day) had an increase more than 60 msec at some time point during the clinical studies. In the ziprasidone group (160 mg/day) it was 1.6%.

Iloperidone and ziprasidone bear a different arrhythmogenic potential. The hERG IC50 values of 29-37 nM for Iloperidone and 56 nM for P88. For ziprasidone hERG IC50 value was 55 nM. Drugs showing a ratio of hERG IC50 and unbound maximum plasma concentration of less than 30 have a high propensity to elicit Torsade de Point arrhythmia. The respective ratio of hERG IC50/free Cmax amount to 8.4-59 for Iloperidone (considering a protein binding of 93-99%, reported in different studies) and 134.5 for ziprasidone (protein binding of 99.9% as described in approval reviews for ziprasidone). More patients discontinued, had a dose reduction/interruption or died due to a cardiac adverse event in the Iloperidone group compared to the ziprasidone group. In addition, heart rate was increased by Iloperidone. In the Phase 3 studies, sinus tachycardia, based on ECG, was reported by 16.9% in the Iloperidone group compared to 9.1% in patients on placebo. There were 6 cases of sudden deaths or deaths due to cardiac AE in the clinical trials. 4423 patients were exposed to Iloperidone → 0.14% of all treated patients died due to sudden death or cardiac AE. In the post-marketing setting there were 33 deaths of which 3 patients died during sleep, 6 were sudden deaths, 6 cases were of cardiac origin.

The metabolism of Iloperidone relies heavily on CYP3A4 and CYP2D6, and significant increases in the exposure of Iloperidone and the active metabolite P88 were observed in patients who are treated with strong inhibitors of CYP3A4 and/or CYP2D6, or who are CYP2D6 slow metabolisers. Accordingly a significant increase in QTc interval was seen in patients who were CYP2D6 poor metabolisers. As discussed in the ad-hoc experts meeting, this could be particularly relevant for patients that are homozygotes for the *4 or *10 allele. The significant effect of CYP2D6 poor metaboliser status warrants genotyping with regard to CYP2D6, with no evidence supporting a safe dose in homozygotes and dose adjustments required in patients who are poor metabolisers. Hypotensive effects were also observed with Iloperidone. The proportion of patients with systolic BP ≤ 90 mmHg or decrease ≥ 10 mmHg in the Phase 3 studies was 25.9% in Iloperidone-treated patients versus 7.2% in placebo-treated patients. The proportion of patients with an orthostatic event (defined as a > 30 mmHg drop in systolic BP) was 13.6% in the Iloperidone group and 6.4% in the placebo group. Iloperidone should be titrated to reduce the risk of orthostatic hypotension due to its alpha-adrenergic antagonistic properties.

Iloperidone was associated with extrapyramidal effects, but to a modest degree. The mean change in Extrapyramidal Symptoms Rating Scale (ESRS) score from baseline to worst score was slightly higher in patients treated with Iloperidone compared to patients on placebo. Akathisia was reported by 4.0% of patients on Iloperidone compared to 2.2% in patients receiving placebo.

Dizziness and sedation occurred in 13.4% and 4.8%, respectively, of patients on Iloperidone, which was more than in patients on placebo.

Iloperidone produces clinically significant weight gain, and the proportion of ≥7% increases were larger than observed with haloperidol, risperidone and ziprasidone. In the Phase 3 studies, the mean change from baseline to endpoint was 1.8 kg in the Iloperidone group and 0.1 kg in the placebo group. The proportion of patients with ≥7% increase was 30.1% (Iloperidone) vs. 9.2% (placebo).

The incidence of hyperglycaemia was higher in the Iloperidone group than in the placebo group and the ziprasidone group, and the incidence increased with exposure and duration of treatment. Shifts in fasting glucose conc. from ≤ 6.1 mmol/L at baseline to > 7 mmol/L during 4-week treatment was 10.8% in the Iloperidone group, 7,1% in the ziprasidone group and 5.9% in the placebo group.

Finally, increased prolactin was observed with Iloperidone, but appears to be less of problem than with risperidone and haloperidol, but not compared to ziprasidone. In the Phase 3 studies, the proportion with elevated prolactin (worst value) was 17.8% in Iloperidone-treated and 7.1% in placebo-treated patient.

3.5. Uncertainties and limitations about unfavourable effects

The main uncertainty relates to the QTc prolongation observed with Iloperidone and – as confirmed by the ad hoc experts' group - to what extent it is associated with serious cardiac outcomes, in particular arrhythmic events such as Torsade de pointes. Few patients who are homozygotes for the *4 and *10 allele have been studied, so any estimate of the effects of Iloperidone on these patients has a significant uncertainty. The CYP2D6 genotype was not known in the patients that died during the clinical studies or post-marketing.

The calculations of the hERG IC50/Cmax ratio heavily rely on the precise estimate of parameters – the unbound plasma concentration and the hERG IC50 – whose estimate actually has a degree of uncertainty.

It is currently unknown if Iloperidone can be safely administered with weak and/or moderate inhibitors of CYP2D6 and/or CYP3A4 considering that the observed QTc prolongation is closely linked to the plasma concentration. It is uncertain whether the measures proposed to minimise the risks – genotyping and frequent ECGs – would be feasible in all settings and if they would in any case be sufficient.

A number of medicines prolong the QT to a varying degree, including certain antidepressants and other antipsychotics. It is unknown if these can safely be co-administered.

Very little information is available from the post-marketing setting. At least one fatal case could possibly have been preceded by ventricular arrhythmia and torsade de pointes There is a least one literature case report of arrhythmia. It is unknown if there could be more.

Another uncertainty relates to longer-term effects on metabolic parameters such, blood glucose and lipids. Available data suggest that Iloperidone causes weight gain and hyperglycaemia (but to a lesser extent dyslipidaemia) in the short-term, but whether a risk of hyperglycaemia is further increased over time is unknown.

Very little is known about the safety and tolerability in elderly patients since very few elderly patients and virtually no very old patients have been included in the clinical programme.

3.6. Effects Table

Table 10 - Effects Table for Fanaptum for the treatment of adults with Schizophrenia.

Effect	Short Description	Unit	Iloperidone	Active comparator(s)	Placebo	Uncertainties/ Strength of evidence	References
Favourable Effects							
PANSS Total	Adjusted mean change from baseline by week 1, LOCF	- (SE)	-4.3 (0.62) (12 mg b.i.d.)	-6.5 (0.87) (ziprasidone)	-4.2 (0.89)	No early separation from placebo in other studies as well.	Study 3101
PANSS Total	Adjusted mean change from baseline by week 4, LOCF	- (SE)	-11.0 (0.96) (12 mg b.i.d.)	-12.0 (1.35) (ziprasidone)	-6.8 (1.38)	p = 0.013 Ilo Vs. Placebo	Study 3101
Maintenance of effect/ Relapse prevention	Number of impending relapses in up to 26 weeks	(%) Number of patients relapsed, (95% CI)	20.4 (12.9, 31.4)		63.4 (52.7, 74.1)	HR (95% CI) 4.7 [2.7, 8.3]	Study 2301
Unfavourable Effects							
Extra-pyramidal symptoms	Mean change in ESRS from baseline to worst score	- (SD)	0.99 (3.4)	1.57 (3.5) (risperidone); 0.94 (3.5) (ziprasidone)	0.64 (2.6)	-	Study Group 1
Akathisia	Objective Assessment of Akathisia Score, patients experiencing worsening	%	17.2	24.5 (risperidone); 27 (ziprasidone); 40.7 (haloperidol)	14.4		Study Group 1
QTc prolongation	Mean change in QTcF	Ms (SD)	15.4 (11.7) (24 mg q.d.)	1.3 (11.1) (quetiapine); 9.6(11) (ziprasidone)	-		Thorough QT study
Hypotension	Patients with systolic BP ⩽ 90 mmHg or decrease ⩾ 10 mmHg	%	25.9	21.1 (risperidone); 7.2 (ziprasidone)	7.2	-	Study Group 1
Body weight increase	Patients with ⩾7% increase	%	30.1	13.0 (risperidone); 8.1 (ziprasidone)	9.2	-	Study Group 1
Glucose levels increase	Shifts in fasting glucose conc. from ⩽ 6.1 mmol/L at baseline to > 7 mmol/L during 4-week treatment	%	10.8	7.1 (ziprasidone)	5.9	-	ISS pooled database, laboratory domain

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Considering all available non-clinical and clinical data (including the thorough QTc study, the overall clinical program and the cases of cardiac-related/sudden unexplained death in clinical trials and post-marketing), iloperidone has a substantial arrhythmogenic potential. The fact that the metabolism of Iloperidone relies heavily on CYP3A4 and CYP2D6 increases the risks of drug-drug interactions and makes the medicine metabolism highly sensitive to genetic polymorphisms.

Emphasis on CYP2D6 genotyping for dose selection could provide a false reassurance to patients who do not carry the mutations. Furthermore, the efficacy of lower doses than 24 mg/ day has not been consistently demonstrated.

The ad hoc expert group recommended that sequential ECGs should be done as they would provide a more reliable indicator of the risk of arrhythmia. This should be done at baseline, during titration to the target dose and thereafter at any dose increase, but also when other medications with effect on QT prolongation or interfering with the pharmacokinetics of Iloperidone are added. Additional periodic ECG evaluations would need to take into consideration a balance between the risks connected to a delayed-appearance of QT prolongation and feasibility and sustainability issues. Furthermore, the treatment setting should include the availability of a cardiologist to support the interpretation of the ECG examinations. Furthermore, it will be difficult to capture any late occurrence of QTc prolongation. In fact, one patient in the clinical development programme had a QTc of more than 500 msec, which occurred more than 3 months after initiation of treatment. Thus risk minimization measures such as CYP2D6 genotyping or extensive ECG monitoring are not considered sufficient to minimize the risk.

The efficacy of Iloperidone in patients with schizophrenia has been documented, but the slow onset of action is a drawback that makes it inappropriate in the treatment of acutely exacerbated patients. Additionally, the estimated magnitude of effect at a population level often appeared lower of the one of active comparators used and the demonstrated efficacy is considered modest.

As discussed by the ad hoc experts group, the profile of Iloperidone might only be of value in chronic, quite stable patients with mild positive symptoms of schizophrenia who need to discontinue their treatment due to debilitating adverse event – in particular EPS symptoms including akathisia. However – as also discussed by the ad-hoc expert group – the use in this population is not supported by specific data and in this setting a worsening of the symptoms cannot be excluded on the basis of the currently available evidence.

Emphasis on CYP2D6 genotyping on the other hand could provide a false reassurance to patients who do not carry the mutations. The ad hoc expert group recommended sequential ECGs should be done as they would provide a more reliable indicator of the risk of arrhythmia. This should be done at baseline, during titration to the target dose and thereafter at any dose increase, but also when other medications with effect on QT prolongation or interfering with the pharmacokinetics of Iloperidone are added. Additional periodic ECG evaluations would need to take into consideration a balance between the risks connected to a delayed-appearance of QT prolongation and feasibility and sustainability issues. Furthermore, the treatment setting should include the availability of a cardiologist to support the interpretation of the ECG examinations.

Extrapyramidal symptoms and akathisia are bothersome side effects of many antipsychotics that significantly affects the quality of life, and akathisia is known to be associated with a higher risk of suicidal behaviour/suicides. Therefore, it must be acknowledged as a clear advantage that Iloperidone appears to be associated with a relatively low incidence of EPS and akathisia when compared to several other marketed antipsychotics.

The hypotensive effects of Iloperidone, including the orthostatic hypotensive effects, are important since they are highly unpleasant to patients and may lead to falls and injuries, especially in elderly subjects. The need to slowly titrate Iloperidone to reduce the risk of orthostatic hypotension is a clear clinical disadvantage, especially as it decreases the time to onset of effect.

The untoward metabolic effects of Iloperidone in terms of weight gain is comparable to that of risperidone. The effects are likely to be maintained or even worsened over time and could very well lead to profound negative consequences for the patient's physical health and overall well-being.

The sedative effects of Iloperidone are quite moderate and could in some clinical situations be an advantage, in other situations a disadvantage.

The effects of Iloperidone on prolactin levels are modest compared to for example risperidone. Symptoms are not trivial and may include sexual dysfunction, menstrual irregularities and gynecomastia.

3.7.2. Balance of benefits and risks

- Considering all available non-clinical and clinical data (including the thorough QTc study, the overall clinical program and the cases of cardiac-related/sudden unexplained death in clinical trials and post-marketing), iloperidone has a substantial and exposure-dependent arrhythmogenic potential. The fact that the metabolism of Iloperidone relies heavily on CYP3A4 and CYP2D6 increases the risks of drug-drug interactions and makes the medicine metabolism highly sensitive to genetic polymorphisms. Risk minimization measures such as CYP2D6 genotyping or extensive ECG monitoring are not considered sufficient to minimize this risk. Hence, the safety of Iloperidone has not been sufficiently demonstrated.
- Furthermore, Iloperidone has a modest efficacy. In addition, it has shown a delayed onset of action, which is a significant concern in the treatment of acute exacerbation of schizophrenia. Therefore, a patient population cannot be identified where the modest efficacy is considered to outweigh the major safety concerns.

Based on the above, the risk-benefit balance of iloperidone is considered negative.

3.8. Conclusions

The overall B/R of Fanaptum is negative.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy for Fanaptum in the treatment of schizophrenia in adults, the CHMP considers by consensus that the safety of the above mentioned medicinal product is not sufficiently demonstrated, and, therefore recommends the refusal of the granting of the marketing authorisation for the above mentioned medicinal product.

The CHMP considers that:

- Considering all available non-clinical and clinical data (including the thorough QTc study, the overall clinical program and the cases of cardiac-related/sudden unexplained death in clinical trials and post-marketing), iloperidone has a substantial and exposure-dependent arrhythmogenic potential. The fact that the metabolism of iloperidone relies heavily on CYP3A4 and CYP2D6 increases the risks of drug-drug interactions and makes the medicine metabolism highly sensitive to genetic polymorphisms. Risk minimisation measures such as CYP2D6 genotyping or extensive ECG monitoring are not considered sufficient to minimise this risk. Hence, the safety of iloperidone has not been sufficiently demonstrated.
- Furthermore, iloperidone has modest efficacy. In addition, it has shown a delayed onset of action, which is a significant concern in the treatment of acute exacerbation of schizophrenia. Therefore,

a patient population cannot be identified where the modest efficacy is considered to outweigh the major safety concerns.

Based on the above, the risk-benefit balance of iloperidone is considered negative.

Furthermore, the CHMP, in light of the negative recommendation, is of the opinion that it is not appropriate to conclude on the new active substance status at this time.

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling, package leaflet, pharmacovigilance system, risk management plan and follow-up measures to address other concerns as outlined in the list of outstanding issues cannot be agreed at this stage.

5. Re-examination of the CHMP opinion of 20 July 2017

Following the CHMP conclusion that Fanaptum was not approvable due to its safety not being properly and sufficiently demonstrated, the applicant submitted detailed grounds for the re-examination of the grounds for refusal.

Detailed grounds for re-examination submitted by the applicant

Unmet need in Schizophrenia treatment

Before addressing the specific issues relating to safety and efficacy, the company provides the following discussion regarding unmet need in schizophrenia treatment in the re-examination response document.

Schizophrenia

Schizophrenia is a chronic and severe mental disorder that affects how a person thinks, feels, and behaves. It is characterized by the presence of positive symptoms (i.e., hallucinations and delusions) and negative symptoms (i.e., blunted affect and social withdrawal), as well as impairment of cognitive functions. People with schizophrenia may seem like they have lost touch with reality, and their symptoms often lead to social isolation. Although schizophrenia is not as common as other mental disorders, the symptoms can be very disabling. Schizophrenia has a worldwide and EU prevalence of approximately 0.5%-1%. The disease can be considered lethal in a significant subset of patients, with suicide being the chief cause of premature death among individuals with schizophrenia. More than 10% of patients with schizophrenia complete suicide in their lifetime. To put that in perspective, 5 million people in the EU alone are likely to be affected by schizophrenia, with 500,000 people at risk for suicide. While significant advances have been made over the last fifty years, none of the treatments available is curative and there remains a significant unmet medical need.

Antipsychotics

Antipsychotic drugs have been the mainstay of schizophrenia treatment for over 60 years. However, many people with schizophrenia given typical or first-generation antipsychotics have experienced suboptimal responses, with disease relapses and disabling adverse effects such as sedation and extrapyramidal symptoms (EPSs)

The treatment algorithm includes different drugs, different doses, or combinations of drug over time to achieve desired symptom relief and tolerability. Furthermore, it can take several weeks to notice an improvement in symptoms. Large nationally sponsored studies of antipsychotic effectiveness such as CATIE in the United States (Clinical Antipsychotic Trials of Intervention Effectiveness; and CUtLASS 1 in the United Kingdome (Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study) have been undertaken to determine the optimal and most cost effective treatments. These extensive studies found

that only 25% of all the participants were satisfied with the level of symptom relief they experienced from their first antipsychotic medication, were able to tolerate its side effects, and stayed on it for the entire 18 months of the study. Over 75% of all participants stopped taking their first antipsychotic medication before the end of 18 months. This was mainly due to side effect tolerability and lack of symptom control. In spite of these treatment shortcomings, it remains very difficult to predict which antipsychotic will work best for each individual patient. Moreover, despite the wealth of data from these and similar longitudinal studies, very few clinically useful outcome predictors have been identified.

It is the goal of future studies to improve prognostic factors that may aid in identifying patient and treatment factors. This would help select treatments that are more likely to succeed, thereby avoiding multiple, unnecessary switches or treatment trials. However, until then, and arguably thereafter too, there will be a need for additional antipsychotic treatments with differentiated efficacy and side effect profiles to help manage this chronic and devastating disease.

Currently, most guidelines recommend second-generation antipsychotics as first-choice treatments in patients with psychotic disorders (National Institute for Health and Care Excellence (NICE, 2014). The class of atypical antipsychotics includes clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, asenapine, lurasidone, cariprazine and brexpiprazole. Drugs in this class share the characteristic of binding both the dopamine and serotonin receptors, but they are also different in the combination of receptors they bind to and their affinity for those receptors. These differences result in unique clinical profiles, especially on aspects of their safety and side effect profiles.

Motor side effects are particularly devastating.

Motor side effects are particularly devastating for schizophrenia patients and balancing between efficacy and side effects is an ongoing challenge. The movement disorders associated with antipsychotics can result in behavioral disturbances (violence and aggression), non- adherence to medication, and exacerbation of psychosis. Involuntary movements (dystonias) are characterized by intermittent or sustained muscle action or abnormal posture and can occur in 25 to 40 percent of patients receiving conventional antipsychotics. Parkinsonian symptoms can develop insidiously within days of starting antipsychotic treatment. The development of Parkinsonian symptoms (muscle rigidity, tremor, bradykinesia, salivation) is dose dependent and occurs in about 20 to 40 percent of patients. These symptoms are categorized as extra pyramidal symptoms (EPS) and different scales are used in schizophrenia and antipsychotic research to try to capture their severity and impact. The drug-induced movements are obvious to an observer and add to the stigma of psychiatric illness and are a significant factor of the risk-benefit assessment made by patients and caretakers.

Akathisia

Akathisia is a particularly debilitating and distressing movement disorder and a serious side effect of antipsychotics. Akathisia is characterized by a feeling of inner restlessness and a need to be in constant motion, and is manifested by rocking while standing or sitting, lifting the feet as if marching on the spot, and crossing and uncrossing the legs while sitting. People with akathisia are unable to sit or keep still, and they tend to fidget, rock from foot to foot, and pace. Many patients often have difficulty describing the pain and restlessness from severe akathisia. Akathisia is distinct from the other motor disorders and is often misinterpreted as an external sign and symptom of the psychiatric disorder. Akathisia is so distressing to patients that its presence is an independent risk factor for suicide in schizophrenia patients. Devastatingly, as many as 90 percent of younger patients taking typical antipsychotics develop akathisia at some time during treatment. In a study of aripiprazole, akathisia occurred in 11 percent of non-schizophrenic patients and led to 1.6 percent discontinuation and other studies have shown akathisia rates of up to 20%.

In spite of its severity and prevalence, the mechanisms underlying akathisia are not well understood. It is postulated that it could be due to dopamine receptor blockade in brain areas other than the striatum or alternatively due to partial agonism at the 5HT1A receptor. The rating scales used to capture the severity of akathisia in patients include the Abnormal Involuntary Movement Scale, Barnes Akathisia Scale, and the Simpson and Angus Scale for EPS. Even with these objective and subjective tools it is difficult to capture how serious and devastating such movement symptoms are to patient's quality of life, and, not surprisingly, they are often cited as a major reason for non-adherence to treatment. Antipsychotic drugs with placebo-like rates of akathisia could be life altering in some schizophrenia patients.

Reasons for non-adherence.

Non-adherence is a significant problem for schizophrenia treatment in general, and specifically for antipsychotics. Approximately 40% of patients are poorly adherent to their antipsychotic medication. Non-adherence to medication has a negative impact on the course of illness resulting in relapse, rehospitalisation, a longer time to remission, and attempted suicide. One reason for non-adherence to antipsychotics is their significant side effects of weight gain, diabetes, dyslipidaemia, extrapyramidal symptoms, akathisia, prolactin elevation, sedation, QTc prolongation, and in the case of clozapine, agranulocytosis. Switching treatments until an acceptable medication is found is the typical way physicians treat psychiatric disorders. Inadequate adherence to antipsychotic medications increases the risk of relapse and associated healthcare utilization and costs. Moreover, with each relapse recovery can be slower and less complete and illness can become more resistant to treatment over time. A review by Sun et al., (2007) estimated that antipsychotic non-adherence in the US was responsible for between $1.4 and $1.8 billion in rehospitalisation costs alone. A drug that minimizes these side effects while delivering equivalent efficacy could make a significant difference in adherence rates and therefore in the lives of patients and in society as a whole.

Conclusion

Patients with schizophrenia and their advocates are looking to improve their subjective well-being, quality of life, and, ultimately their day to day functioning in society. There is great need for additional therapy that can be used to control patients in the both the acute and throughout the residual phases of schizophrenia. Schizophrenia Patient groups in both the U.S and the EU, such as the National Alliance on Mental Illness (NAMI), Global Alliance of Mental Illness Advocacy Networks-Europe (GAMIAN), European Federation of Associations of Families of People with Mental Illness (EUFAMI), are advocating for "balanced" treatments with a pharmacodynamic profile that addresses the need for efficacy without compromising psychiatric or physical well-being. After years of trying to find the optimal medication, many patients are left without many options. New drug options with improved tolerability and subjective acceptability are extremely important to patients and would promote adherence to and satisfaction with their treatment. The Applicant believes Fanaptum can be a useful option in the EU and EAA and beneficial for (i) patients in an acute schizophrenia episode who cannot stabilize on another medication due to tolerability issues and (ii) previously stabilized patients who have subsequently developed tolerability issues and would like to switch antipsychotic medication for long-term maintenance.

Ground #1

- Considering all available non-clinical and clinical data (including the thorough QTc study, the overall clinical program and the cases of cardiac-related/sudden unexplained death in clinical trials and post-marketing), iloperidone has a substantial and exposure-dependent arrhythmogenic potential. The fact that the metabolism of Iloperidone relies heavily on CYP3A4 and CYP2D6 increases the risks of drug-drug interactions and makes the medicine metabolism highly sensitive to genetic polymorphisms. Risk minimization measures such as CYP2D6

genotyping or extensive ECG monitoring are not considered sufficient to minimize this risk. Hence, the safety of Iloperidone has not been sufficiently demonstrated.

In this section, the applicant addresses concerns about the CHMP's assessment of the arrythmogenic potential of iloperidone, in particular its potential to prolong the QTc interval. The Applicant then describes measures than can be taken to further minimize the risk. The measures include modifying the therapeutic indication, recommending a new treatment algorithm, and introducing additional risk mitigation measures. The Applicant discusses the evidence to support the view that the risk is mild/moderate and manageable, and make the case that the overall benefit risk profile for Fanaptum is favorable. The Applicant believes that these measures are feasible and in alignment with EMA safety and pharmacogenomic guidelines.

Assessment of arrythmogenic potential of iloperidone

Preclinical studies

The CHMP has discussed and asked for clarity regarding iloperidone's ability to inhibit the hERG portion of the inward-rectifying potassium channel of the heart. It is well known that studying cells transfected with the hERG (human ether-a-go-go-related) gene can help to assess and stratify the risk that the compound in question may cause QTc prolongation and result in possible repolarizing anomalies. It is also hypothesized that the ability of a given drug to inhibit potassium current in these transfected cells, also in consideration of the maximal free concentration of the agent in the blood of humans, can further help to understand the potential risk of this drug to produce repolarizing anomalies, including the propensity to cause torsades de pointes. This consideration is referred to as the determination of the hERG/free IC50 ratio, which was specifically highlighted in the CHMP assessment of iloperidone. In Redfern et al., it is proposed that drugs that display a 30-fold ratio of hERG IC50 over the free Cmax, may have lower propensity for inducing such ventricular tachycardia arrhythmias. The Applicant agrees with the CHMP that these calculations are sensitive to several factors including the hERG binding affinity measurements and the calculation of free or unbound drug. Vanda's calculations are strictly derived from studies submitted in the dossier, i.e., hERG binding for iloperidone, P88 and ziprasidone from the same study, concentrations for each from study 2328, and protein bound fractions from study XS-0531.

In study 008167, "Functional Block by ILO522, ILO522 P95-12113 metabolite, ILO522 P88-8991 metabolite in comparison to Risperidone, and Ziprasidone on Cloned hERG Channels Expressed in Mammalian Cells" the IC50 of iloperidone and P88 were found to be 29 nM and 56 nM, respectively.

To determine the Cmax level, the Applicant used the study "ILO522-2328: A randomized, open-label, multicenter, 5-arm, safety study evaluating the effect of oral iloperidone at doses of 8 mg b.i.d., 12 mg b.i.d., and 24 mg q.d. on QTc interval duration in the presence and absence of metabolic inhibition, relative to other antipsychotics (ziprasidone 80 mg b.i.d, and quetiapine 375 mg b.i.d., in the presence and absence of metabolic inhibition), in otherwise healthy patients diagnosed with schizophrenia or schizoaffective disorder." This study showed that the Cmax values of iloperidone and P88 were, 21ng/ml (MW: 427) and 24 ng/ml; (MW: 431), respectively.

To determine the percent-bound fraction, the Applicant used data from the study, "Study XS-0531: In vitro assessment of iloperidone and metabolites P88 and P95 protein blinding in human plasma." This study showed that the percent bound fraction of iloperidone is 99% and of P-88 is 98%.

The resulting hERG IC50 / free Cmax ratio is 59 for iloperidone and 49 for P88.

These results are summarized again in the table below:

Preclinical hERG IC50 values

Medication	hERG IC50 (nM)	Cmax (ng/ml)	MW	% bound	hERG IC50/ free Cmax ratio*
Iloperidone	29	21	427	99	59
P88	56	24	431	98	49

*(hERG IC50) / (((Cmax/MW)*1000) * ((100-%bound)/100))

According to the Applicant, this analysis demonstrated the effect of iloperidone and ziprasidone on the magnitude of QTc prolongation appear to be identical. The Applicant notes the discrepancy of hERG IC50 discussed during the assessment process using a more conservative approach. QTc data are hard to compare across studies due to differences in species and experimental protocols. Regardless of calculation of predicted risk, the most important evidence is what happens in the clinic. These studies are in vitro predictive models and do not fully reflect the Applicant's post marketing experience. This ratio is meant to predict what will happen if a drug with a given ratio was to be developed and marketed. Fanaptum has been marketed for 7 years and there is no evidence of excess cardiac mortality or incidence of TdP. Thus even if there might have been theoretical grounds for suspecting that the drug may be arrhythmogenic, the evidence thus far suggests that it is most likely not. However the data is interpreted, the Applicant believes that their new treatment algorithm mitigates the non-zero risk of Fanaptum treatment with regard to QT prolongation. The Applicant believes this makes Fanaptum a potential second-line option to treat schizophrenia.

Thorough QTc study

The QTc prolonging effect has been studied in several clinical studies, including a thorough QT study (Study 2328), which showed that iloperidone prolongs the QTc interval by 8.5 msec at 8mg bid and by 9msec at 12mg bid (largest dose recommended). Changes in QTcF were similar to changes observed in patients treated with ziprasidone (~9 msec) and higher than mean changes observed in patients treated with quetiapine (1~msec). With the addition of CYP2D6 inhibitors, iloperidone prolonged the QTcF by 11.2ms at 8mg BID and by 11.6 msec at 12mg BID. With the addition of both CYP2D6 and CYP3A4 inhibitors, QTcF was prolonged by an average of 15.7 msec at 8mg BID and by 19.5 msec at 12mg BID (Study 2328, Table 9-2). When the metabolic inhibitors were added in addition to iloperidone, the drug exposure only increased to a maximum of 2.3-fold and the QTcF interval increased by approximately 15 msec. The data on drugs that prolong the mean QT/QTc interval by more than around 5 and less than 20 msec are inconclusive, but some of these compounds have been associated with proarrhythmic risk. Drugs that prolong the mean QT/QTc interval by >20 msec have a substantially increased likelihood of being proarrhythmic, and might have clinically important arrhythmic events captured during drug development (ICH E14 guidelines). The Applicant thinks this constitutes a moderate QT prolongation propensity for iloperidone and acknowledges that while it theoretically may add to cardiac risk, no QT related cardiac arrhythmias have been seen in the clinical program.

Regulatory guidelines have suggested that absolute QTcF values of greater than 500 msec and QTcF increases of greater than or equal to 60 msec are of clear clinical concern (CPMP guidelines). In trial 2328, no patients in any treatment arm experienced a QT or QTc (using any correction factor) value of greater than 500 msec. Seven patients in the iloperidone treatment arms experienced a change in QTc value of > 60 msec at Tmax (10 patients overall in all secondary analyses). No patients in the quetiapine or ziprasidone treatment arms experienced changes of this magnitude. Therefore, although mean changes in QTc suggest iloperidone and ziprasidone have an effect on cardiac repolarization, according to the

Applicant the effect does not appear to cause a substantial number of patients to cross thresholds that are considered of clear clinical concern. The Applicant believes that risk-mitigating steps can be taken as proposed in order to further reduce any potential cardiac risk.

In addition, the Applicant has studied and demonstrated in two clinical studies that individuals with CYP2D6 genotypes that are associated with reduced enzymatic activity have higher exposures to iloperidone and the active P88 metabolite and have higher QTc prolongation on average than those individuals with polymorphisms associated with extensive metabolizer status of CYP2D6.

The exploratory pharmacogenetic evaluations included in Study 2328 were designed to investigate the association between genotypes and phenotypes. Single nucleotide polymorphisms (SNPs) in the CYP2D6 gene were associated with different levels of QT prolongation after iloperidone treatment. At the G1846A locus, normal CYP2D6 metabolizer have the *1/*1 genotype, if an individual has a genotype of *1/4 or *4/4 they have a higher average QT (11.1 vs 18.5 msec). At the C100T locus, individuals that differ from *1/*1 with a *1/*10 or a *10/*10 genotype also have a higher than average QT (10.8 vs 19.2 msec)

QTcF prolongation in CYP2D6 genotypes from Study 2328

CYP2D6 SNP	CYP2D6 SNP	n	ΔQTcF	P value
G1846A	*1/*1	52	11.1	0.05
	*1/*4 or *4/*4	16	18.5	
C100T	*1/*1	54	10.8	0.02
	*1/*10 or *10/*10	17	19.2	

It is well known in the literature and in practice that a prolonged QTc interval can be associated with ventricular arrhythmias including ventricular tachycardia and torsades de pointes and elevates the risk level for patients. However, an increase in mortality or cardiac severe events has not been seen in the iloperidone treated population.

CYD2D6 and CYP3A4 inhibitors

In regards to CYP3A4 metabolism of iloperidone, the administration of a strong CYP2D6 inhibitor in Period 2 and the coadministration of a strong CYP3A4 inhibitor in Period 3 of study 2328 resulted in increases of Cmax of only 1.6 to 2.3 fold at the maximum recommended dose of 12 mg BID. This moderate increase suggests a ceiling of increase in exposure under the worst possible inhibition of the metabolism of iloperidone. The Applicant does not have data on CYP3A4 inhibitors alone. It should therefore be expected that milder circumstances with weak or moderate inhibitors of these enzyme systems will result in minimal changes in exposure of no clinical significance. For other drugs where strong inhibitors may increase exposure of the test substance by 10-20 fold, the concern for weak or moderate inhibitors is valid; however, these conditions do not apply to iloperidone. Because there is a non zero risk profile for QT prolongation with iloperidone, the Applicant proposes to contraindicate strong CYP2D6 and strong CYP3A4 inhibitors and also recommends lower dose adjustments for mild inhibitors of these enzymes.

During the clinical program, there have been 16 reported fatal outcomes out of 4540 patients, encompassing 2530 patient-years of exposure. 6 of these 16 fatal outcomes were determined by the

CHMP to be of possible cardiac etiology. This corresponds to a cardiovascular mortality rate of 237/100,000 patient years and an all-cause mortality of 632/100,000 patient years.

The Applicant compared these rates against those reported by Olfson et al. In this paper, the authors report mortality rates from a schizophrenia cohort that included 1,138,853 individuals, 4,807,121 years of follow-up, and 74,003 deaths, of which 65,553 had a known cause. The cohort included schizophrenia patients from the Medicaid program ages 20 – 64 years old. This paper reported that the cardiovascular mortality rate of schizophrenia patients was 403/100,000 patient-years and the overall mortality rate was reported to be 1539/100,000 patient years. This is approximately 3.6 and 3.7 times the general population rates for cardiovascular and all-cause mortality, respectively.

Given that the mortality rates based on the clinical program correspond to lower rates than those seen in this population study, the Applicant believes that there is no excess mortality in the iloperidone clinical program for either cardiovascular or all-cause mortality.

Cardiac mortality in post-marketing data

With regards to the known cardiac risk of iloperidone, in the post-marketing period of approximately 71,000 patient-years, there have been no reports of ventricular tachycardia or torsades de pointes.

The Applicant has similarly analyzed the mortality rates as seen through pharmacovigilance in the post-marketing period. The Applicant based their analysis on 14 possible cardiovascular deaths (i.e. as identified by the CHMP Rapporteur during the assessment) out of a total of 33 reported fatal outcomes during the post-marketing period. Given an approximate 71,000 patient year exposure in the post-marketing period, they calculated the mortality rates per 100,000 patient years. They have used underreporting rates of 85%, 90% and 95% consistent with those reported by Hazell et al..

Using the most conservative rate of under-reporting of 95%, the cardiovascular mortality rate is estimated to be 394/100,000 patient years of exposure and the overall mortality rate is estimated at approximately 930/100,000 patient years.

Similarly, as these estimated rates are lower than those seen in the population study of Olfson et al. 2015, the Applicant believes that there is no excess mortality in the iloperidone post-marketing period for either cardiovascular or all-cause mortality

Risk mitigation measures

To address the CHMP safety concerns the Applicant has:

- Modified the therapeutic indication to second-line treatment for schizophrenia
- Proposed additional risk mitigation measures:
- CYP2D6 genotyping before starting iloperidone treatment
- Contraindication in CYP2D6 poor metabolizers
- Contraindication in patients at risk for at risk of QT prolongation and cardiac arrhythmia, and congenital QT prolongation
- Initiation of iloperidone treatment in clinical settings where the patient can be monitored by ECG
- Sequential monitoring with ECG with dose increase and as appropriate
- Contraindication for patients on strong CYP2D6 inhibitors
- Dose adjustments for patients on CYP3A4 inhibitors

To address the CHMP safety concern the Applicant proposes that Fanaptum be used only in known CYP2D6 extensive metabolizers. The Applicant proposes that treatment initiation on iloperidone should be done in a setting where the patient can be monitored and an ECG can be performed at approximately 2 hours after administration of the medication. 2 hours is the approximate Tmax of iloperidone and P88, the active metabolite, which are both associated with QTc prolongation. The Applicant proposes to perform ECG at Tmax because QTc prolongation was shown to be at maximum risk when the QTc-prolonging agent is at its maximal blood concentration. This is the same method used throughout their QT monitoring study.

ECG's should be taken at Tmax on every day of titration. This would require a patient to come into the clinic for the entire titration period, which will take 4 days. After the titration period, and the patient is on a stable dose, the Applicant proposes that the ECG's be done weekly during the first month of treatment, and when the dose is increased.

Genotyping Feasibility

Genotyping to test CYP2D6 poor metabolizer status in practice fits the proposed Fanaptum SmPC language well. CYP2D6 variation is one of the most well known drug-metabolism genetic interactions, and as such has become available at a number of laboratories across Europe. Post-approval in the USA, Vanda has provided sampling kits to hundreds of physicians and health care providers to help raise awareness and education around this genotype, and would plan to do the same in Europe. Sampling kits for taking buccal swab or other sample are light-weight, small, convenient to store, and have a long shelf-life, and easy to ship to a central or distributed lab in the European Union that can perform the genotype service. Although expedited service is sometimes available, a genotype report typically can be returned to the physician in approximately one week to assess status. In some cases, because literature has elaborated on CYP2D6 interacting with multiple psychiatric medications, the patient may already have had their genotype determined as well. Based on the results of the test, the health care provider can then use that based on the Fanaptum SmPC instructions.

In regards to the CYP2D6 genotyping, the Applicant has identified several companies across Europe where CYP2D6 testing can be performed. Alternatively, with the guidance of the EMA, they also offer that Vanda can coordinate the accessibility of this genotype test in coordination with a central laboratory vendor. This is a risk-mitigation strategy that has been successfully used by several companies, including Amgen for Vectibix (panitumumab), an epidermal growth factor receptor antagonist, in which the company has ensured the availability of the testing kit. The Applicant's measure to genotype patients before treating them with Fanaptum is consistent with the pharmacogenomics guidelines of the EMA. (Examples of central laboratories that perform CYP2D6 can be found in Appendix 1)

Modified indication + treatment algorithm

The Applicant considers two scenarios where Fanaptum may be a useful treatment.

- Schizophrenia patients who are stabilized, but because of poor tolerability or suboptimal efficacy need to switch to another antipsychotic medication.

For example, a patient whose symptoms were successfully stabilized with antipsychotic X, but over time develops akathisia and is willing to taper off.

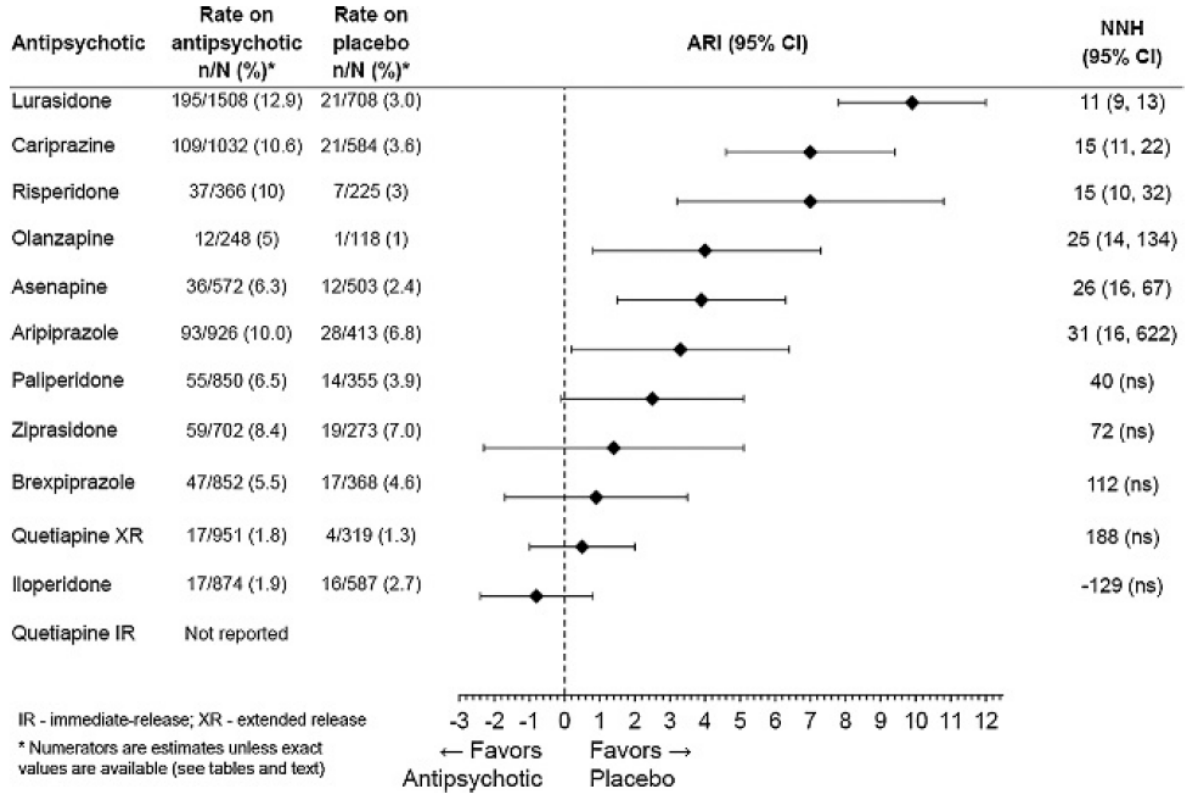
- Schizophrenia patients in acute distress and unable to be stabilized on another antipsychotic medication for tolerability reasons.

For example, the patient in an acute episode of schizophrenia is unable to tolerate the full titration of antipsychotic Y and therefore not fully stabilized.

A physician may then want to consider switching either of those patients to Fanaptum. The physician would check baseline ECG, cardiac risk potential, send out for a genetic test along with other laboratory tests or check if CYP2D6 genotype is known. The physician can begin to wean the patient off other antipsychotics. When test results have come back and the patient is genotyped as a CYP2D6 extensive metabolizer, the physician can begin the titration of Fanaptum with ECG monitoring. In the Applicant's opinion, the patient is not at increased risk for relapse during down titration of other antipsychotic because on average, on placebo, the time to relapse is 79 days. They also think the delay in efficacy onset will be acceptable to the physician and patient given the tolerability issues with other antipsychotics. Moreover, switching to other medications is considered typical clinical practice in treating psychiatric disorders.

The Applicant also referenced a paper by Citrome (2017) in support of the better tolerability of Iloperidone - in particular in terms of incidence of Akathisia – with other drugs in the therapeutic context.

ARI and NNH and 95% CIs for Akathisia (Citrome, 2017).



The Applicant believes that this treatment algorithm can greatly reduce the risk of prolonging the QTc interval, as there are both preventive measures (CYP2D6 genotyping) and monitoring measures (ECG's). The Applicant thinks any QT prolongation will be seen at Tmax and is unlikely to get more severe over time or occur unexpectedly. In fact, in the 4 week QT study, an adaptation to QT prolongation was observed. By the end of 4 weeks QT prolongation was 5 msec on average. Any cases of later post-marketing QT prolongation that were observed were assessed as not likely to be attributed to iloperidone.

In summary, using several conservative approaches, the Applicant has not been able to identify an increased cardiac safety risk in iloperidone treated patients. Furthermore, the Applicant believes that the above-outlined risk mitigation strategy in combination with the observed safety evidence of iloperidone provide for a risk profile that can be effectively managed in the clinical setting in Europe.

Ground #2

- Furthermore, Iloperidone has a modest efficacy. In addition, it has shown a delayed onset of action, which is a significant concern in the treatment of acute exacerbation of schizophrenia. Therefore, a patient population cannot be identified where the modest efficacy is considered to outweigh the major safety concerns.

The Applicant addresses the CHMP's concerns about (i) modest efficacy, (ii) a delayed onset of effect, (iii) a maintenance benefit, and (iv) the identification of a patient population that can benefit from Fanaptum. They begin with study 3101, and then describe the supporting short-term studies 3000, 3004, 3005, as well as phase 4 studies, and in the process try to address the CHMP's stated concerns about short term efficacy and delay in onset of effect. They then discuss their long term study 2301 for the prevention of schizophrenia relapse, and address the CHMP's concerns regarding patient stabilization. Finally, they identify a patient population that can benefit from Fanaptum.

<u>Short-Term Efficacy - Pivotal Study 3101</u>

- Study 3101 was designed to (i) demonstrate that iloperidone 24 mg/d (12 mg BID) is superior to placebo and (ii) to allow the inspection of the relative effect versus an active control of a similar titration schedule. Study 3101 was successful as it showed iloperidone's superior effect over placebo and showed that iloperidone's effect was almost identical numerically to that of ziprasidone.
- In Study 3101, the primary end point was change from baseline at Week 4 in PANSS-T score based on the MMRM analysis. The 24mg/d group was statistically superior compared to the placebo group (p=0.006). This study confirmed the hypothesis that iloperidone is an effective antipsychotic with similar potency to another marketed agent for treating schizophrenia.

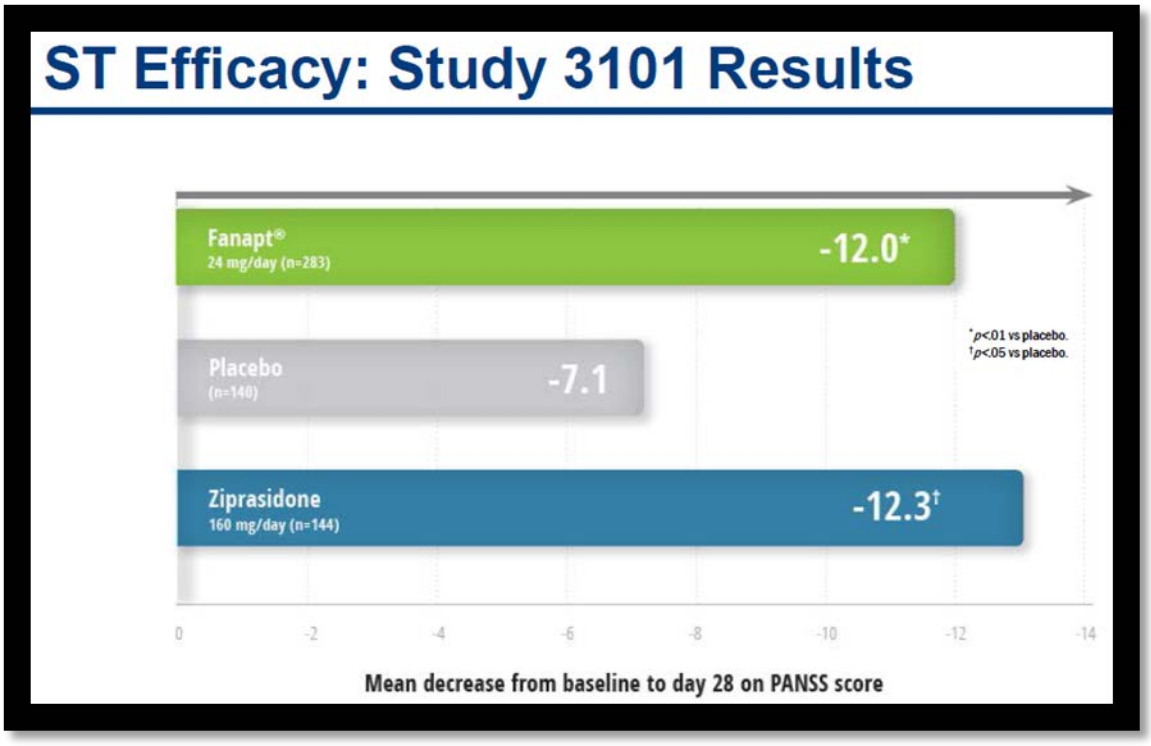


Figure 3 Short Term Efficacy Results of Study 3101. Mean decrease from baseline to week 4 on PANSS score in Fanapt, placebo and ziprasidone.

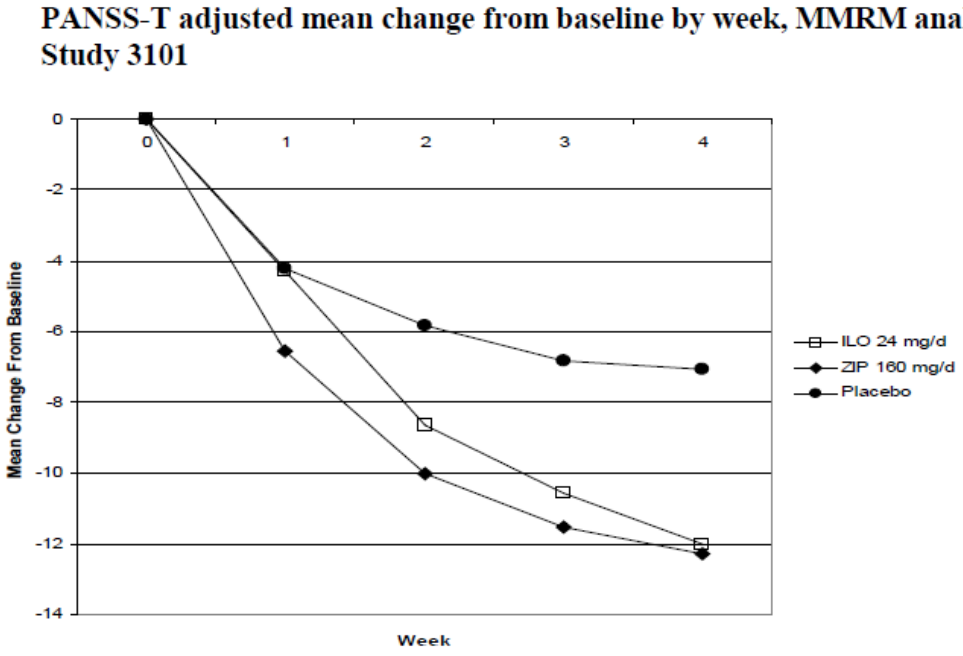


Figure 4 PANSS-T mean change from baseline in Fanaptum (ILO), Ziprasidone (ZIP) and Placebo (PBO) treated patients

Supportive Studies

As noted earlier, two of the Phase III studies, Study 3004 and Study 3101, met the protocol specified primary efficacy endpoint and are considered positive studies and the main source of efficacy data. According to the Applicant, it is important to note that the remaining Phase III studies, namely Study

3000 and Study 3005, while not meeting the protocol specified primary efficacy endpoint and being considered negative studies for regulatory purposes, had at least one dose or dose range that was statistically superior to placebo in each.

Studies 3000, 3004 and 3005 were of six weeks duration and aimed to examine the ability of iloperidone to improve the symptoms of an acute exacerbation of schizophrenia symptoms. To ensure that the clinical trial was successfully conducted, a positive control was included in each of the studies. For study 3000 this control was the antipsychotic haloperidol, while studies 3004 and 3005 included risperidone as a positive control. None of these studies were designed as comparative efficacy studies.

Study 3000 included three doses of iloperidone, namely 4mg/d, 8 mg/d and 12 mg/d. As a primary endpoint the effect of the combined 8mg/d and 12 mg/d was pre-specified. While the primary endpoint showed a trend of improvement, it did not reach statistical significance. However, the 12 mg/d group showed superiority to placebo when analyzed separately.

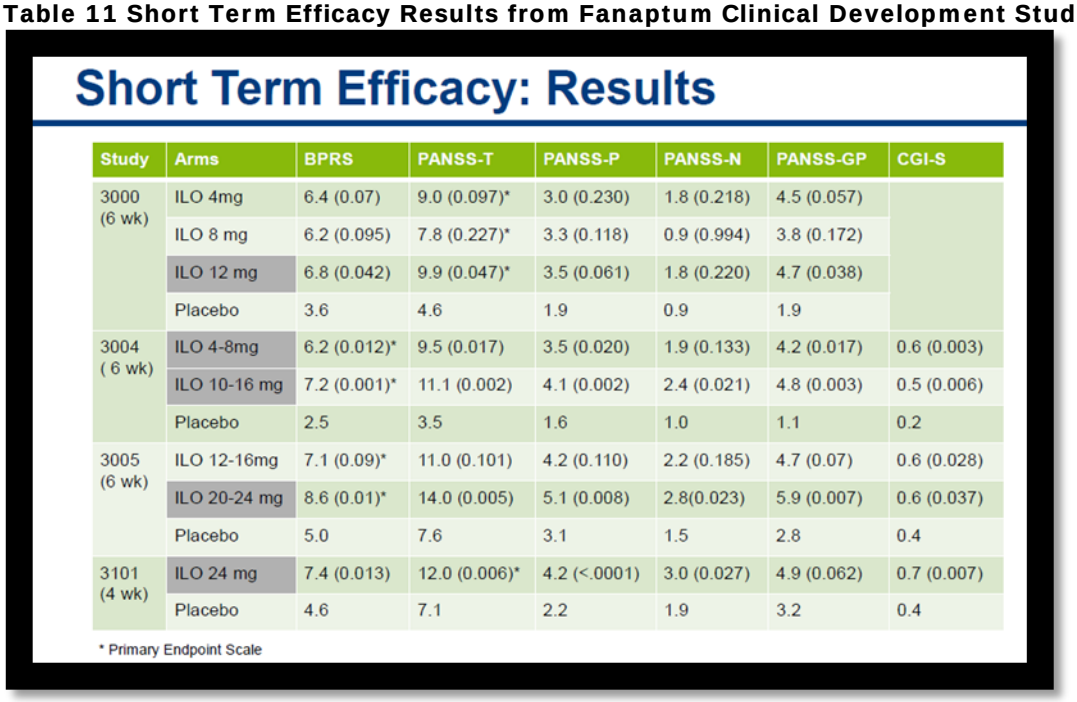
Study 3004 was designed with two iloperidone arms. The first arm was a flexible dose range of 4-8 mg/d and the other was a 10-16 mg/d range. In this study the 10-16 mg/d was the pre-specified arm for the primary endpoint analysis and succeeded to significantly separate from placebo. The lower dose 4-8 mg/d arm also separated from placebo. For Study 3004, mean change from baseline in BPRS score at Week 6 based on the LOCF analysis in the iloperidone 10-16 mg/d group was statistically superior compared to the placebo group (p=0.001).

Study 3005 was designed to evaluate the effects of two dose ranges 12-16 mg/d and 20-24 mg/d. The 12-16 mg/d was the pre-specified primary endpoint arm and it failed to significantly separate from placebo although it demonstrated a strong trend. The 20-24 mg /d arm did separate from placebo in a statistically significant manner (p=0.01).

Comparative Efficacy (Concern about Iloperidone having a modest effect)

The Applicant has previously said that earlier studies were not designed to directly compare iloperidone to the active controls, but only to ensure the studies were appropriately designed. The Applicant states that titration period and delayed onset of action give active controls a “head start” in these studies and make it appear that iloperidone is less effective than the active controls.

Table 11 Short Term Efficacy Results from Fanaptum Clinical Development Studies



Short Term Efficacy: Results

Study	Arms	BPRS	PANSS-T	PANSS-P	PANSS-N	PANSS-GP	CGI-S
3000 (6 wk)	ILO 4mg	6.4 (0.07)	9.0 (0.097)*	3.0 (0.230)	1.8 (0.218)	4.5 (0.057)	
	ILO 8 mg	6.2 (0.095)	7.8 (0.227)*	3.3 (0.118)	0.9 (0.994)	3.8 (0.172)	
	ILO 12 mg	6.8 (0.042)	9.9 (0.047)*	3.5 (0.061)	1.8 (0.220)	4.7 (0.038)	
	Placebo	3.6	4.6	1.9	0.9	1.9	
3004 (6 wk)	ILO 4-8mg	6.2 (0.012)*	9.5 (0.017)	3.5 (0.020)	1.9 (0.133)	4.2 (0.017)	0.6 (0.003)
	ILO 10-16 mg	7.2 (0.001)*	11.1 (0.002)	4.1 (0.002)	2.4 (0.021)	4.8 (0.003)	0.5 (0.006)
	Placebo	2.5	3.5	1.6	1.0	1.1	0.2
3005 (6 wk)	ILO 12-16mg	7.1 (0.09)*	11.0 (0.101)	4.2 (0.110)	2.2 (0.185)	4.7 (0.07)	0.6 (0.028)
	ILO 20-24 mg	8.6 (0.01)*	14.0 (0.005)	5.1 (0.008)	2.8(0.023)	5.9 (0.007)	0.6 (0.037)
	Placebo	5.0	7.6	3.1	1.5	2.8	0.4
3101 (4 wk)	ILO 24 mg	7.4 (0.013)	12.0 (0.006)*	4.2 (<.0001)	3.0 (0.027)	4.9 (0.062)	0.7 (0.007)
	Placebo	4.6	7.1	2.2	1.9	3.2	0.4

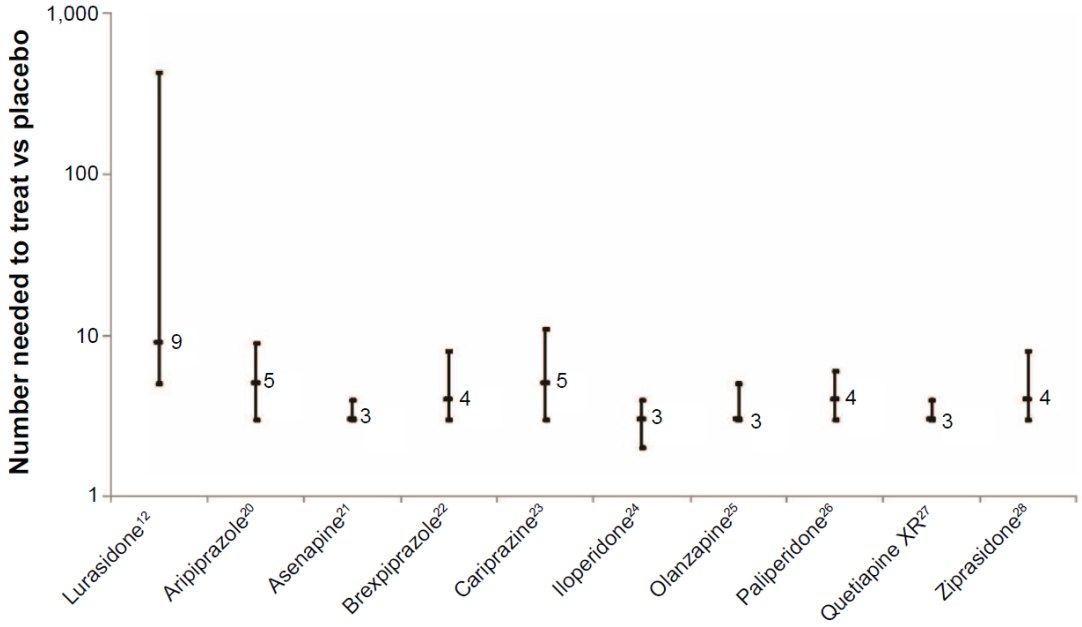
* Primary Endpoint Scale

The appearance that the active controls performed better led the Applicant to examine the results more closely in order to better understand the reasons behind this appearance of a lower magnitude of effect by iloperidone. Study 3005 was the largest study conducted and lends itself to further exploratory analysis. In this study, the randomization schema was 2:1:1:1 for iloperidone 12-16 mg/d, iloperidone 20-24 mg/d, risperidone and placebo, respectively. The Applicant recognized that the two iloperidone arms had 10-15% more dropouts than risperidone during the first two visits. It was also true that the titration schema required a two week titration for iloperidone but not for risperidone. In a post-hoc analysis of patients taking iloperidone for over 2 weeks (75%-85%) and therefore getting a full “treatment”, the effect of iloperidone appeared to be almost identical to that of risperidone. This suggested to the Applicant that the appearance of inferiority was not an individual patient level but rather at a population level as fewer patients had the opportunity of response. This observation was not observed in the meta-analysis of study 3004 under the same two week population. The Applicant believes that this variability is, however, not surprising given the post-hoc nature of the analysis and the non-controlled nature of the experiment.

Large studies such as CATIE and CUTLASS as well as studies endorsed by World Health Organization (WHO) and the WHO Mental Health Gap Action Programme (mhGAP) has tried to rank the efficacy of all antipsychotics on the market. A WHO endorsed large scale meta-analysis that compared efficacy and tolerability of approved antipsychotics on the market included iloperidone in the analysis. These studies concluded that second generation antipsychotics differed substantially in side-effects, but demonstrated only small differences in efficacy. Therefore, the WHO endorses that there is no clinically relevant advantage of one second-generation antipsychotic over others and choice should be based on availability, cost, patient preferences and possible adverse effects associated with each medication. Iloperidone has shown to be similarly effective in treating schizophrenia, although it may have a titration disadvantage. The Applicant believes that this still makes it a useful tool to treat a chronic disease where many antipsychotics have to be tried before the optimal one is found.

In addition, the Applicant provided an indirect comparison of the NNT for prevention of relapses with SGAs referencing a paper by Citrome (2016).

NNT vs placebo and 95% CI for the outcome of relapse (or impending relapse) for available data from the pivotal placebo-controlled randomised withdrawal studies of the oral first-line SGAs. (Citrome, 2016)

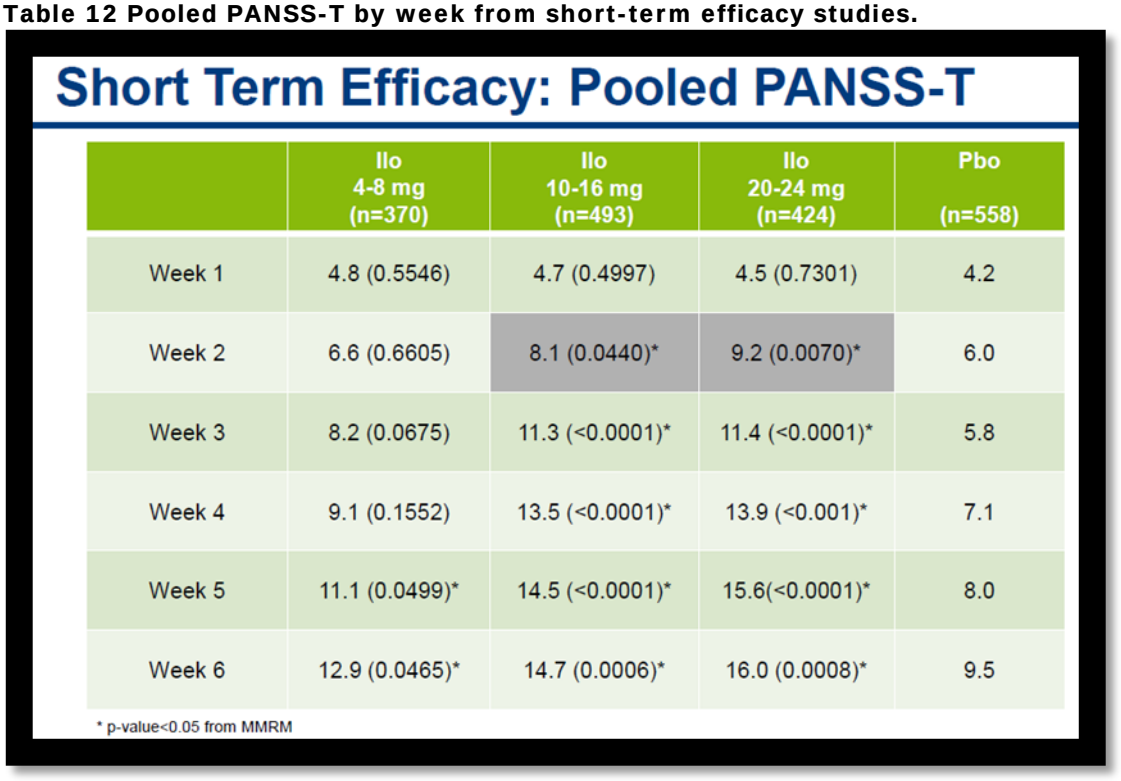


Delayed onset of action

The Applicant acknowledges the concern that Fanaptum has a delayed onset of efficacy due to the need for drug titration. Therefore, they do not recommend Fanaptum as a first line treatment in an acute exacerbation of schizophrenia. Titration is used for some antipsychotics in order to improve initial tolerability and treatment adherence. When titration is necessary for a drug, this of course increases the length of time before steady state, and therefore introduces a delay before a therapeutic effect is achieved. Nevertheless, this practice is used with many psychiatric drugs, including other antipsychotic drugs, and they believe is a well-established practice. For ilpoperidone in particular, they believe that they have proposed an approach to initiating treatment in a clinical setting where such titration can be safely and effectively accomplished. This would include daily titration, symptom monitoring, and ECG monitoring, and the Applicant believes that any delay of efficacy onset due to drug titration would not put the patient at increased risk if the patient and physician decide that iloperidone is an appropriate treatment for their schizophrenia after trying and failing on other treatments.

The Applicant has been asked to define Fanaptum's onset of action and demonstrated in their studies significant differences at doses 12-24mg/day at 2-3 weeks (Table 12). However, their studies were never designed to find out how fast is the onset of action but rather the primary end point effect at 6 or 4 weeks of treatment. This is what they understand to be the EMA's guidance for the development of drugs for schizophrenia. The guidance suggests that shorter duration of studies are not advisable as they may be falsely negative or they may not examine the stability of the effect over time. By definition drugs that require a period of titration will need more time to take effect. Among approved antipsychotic treatments there are already differences of timing to reaching an effective dose. Such a "delay" to reach an effective dose does not mean that the final effectiveness of a test drug is lower. In light of their new indication, they believe a delay in onset is no longer an issue.

Table 12 Pooled PANSS-T by week from short-term efficacy studies.



Short Term Efficacy: Pooled PANSS-T

	Ilo 4-8 mg (n=370)	Ilo 10-16 mg (n=493)	Ilo 20-24 mg (n=424)	Pbo (n=558)
Week 1	4.8 (0.5546)	4.7 (0.4997)	4.5 (0.7301)	4.2
Week 2	6.6 (0.6605)	8.1 (0.0440)*	9.2 (0.0070)*	6.0
Week 3	8.2 (0.0675)	11.3 (<0.0001)*	11.4 (<0.0001)*	5.8
Week 4	9.1 (0.1552)	13.5 (<0.0001)*	13.9 (<0.001)*	7.1
Week 5	11.1 (0.0499)*	14.5 (<0.0001)*	15.6(<0.0001)*	8.0
Week 6	12.9 (0.0465)*	14.7 (0.0006)*	16.0 (0.0008)*	9.5

* p-value<0.05 from MMRM

In Study 3004, where risperidone served as the positive control, there were significant differences between iloperidone and risperidone with respect to length of titration (longer for iloperidone). The target dose of iloperidone was achieved in a week while the therapeutic dose of risperidone was achieved on Day 2. Given the long half-life of iloperidone (~18 hours), steady-state was not achieved for several additional days. However, this study reached its primary end point at week 6 and separation from placebo began at week 3 vs week 1 for risperidone (Table 13). In study 3101, the primary end point was reached at week 3 and separation from placebo began at week 3 compared to week 2 for ziprasidone (Table 14). Like some other approved antipsychotics, iloperidone requires titration to an effective dose and may not have its full therapeutic effect within the first few days of treatment. The Applicant believes that this does not make iloperidone an inferior drug, just a slower acting drug. In the context of a chronic, life-long disease, the Applicant doesn't believe that this 1-week delay imposes significant risk to the patient.

Table 13 LOCF analysis of primary Variable BPRS adjusted mean change from baseline by week in study 3004

Timepoint	ILO 4-8 mg/d n=143		ILO 10-16 mg/d n=149		RIS 4-8 mg/d n=146		Placebo n=152
Baseline (SD)	54.9 (8.8)		54.1 (9.1)		54.7 (10.0)		54.2 (9.8)
Week 1	-3.7	p=0.411	-3.5	p=0.546	-5.4*	p=0.018	-2.8
Week 2	-4.8	p=0.529	-5.5	p=0.232	-7.9*	p=0.001	-4.0
Week 3	-4.8	p=0.190	-6.4*	p=0.009	-8.8*	p<0.001	-3.0
Week 4	-5.6*	p=0.050	-6.7*	p=0.005	-10.1*	p<0.001	-2.8
Week 5	-6.1*	p=0.005	-6.7*	p=0.001	-10.2*	p<0.001	-2.1
Week 6	-6.2*	p=0.012	-7.2*	p=0.001	-10.3*	p<0.001	-2.5

N=number of patients; ILO=iloperidone; RIS=risperidone

*** p<0.05 (two-tailed) compared with placebo; based on t test using ANCOVA model.**

Note: Change is calculated as post-baseline minus baseline value, where negative change reflects improvement and positive change reflects worsening on the scale. Adjusted change = Least squared mean change from the ANCOVA model (including treatment, center, baseline and the treatment-by-baseline).

Source: ILP3004 CSR Post-text Table 9.1-2

Table 14 MMRM analysis of Primary Variable PANSS-T adjusted mean change from baseline by week in study 3101

Timepoint	ILO 24 mg/d n=283		ZIP 160 mg/d n=144		Placebo n=140
Baseline (SD)	92.9 (13.1)		90.9 (11.5)		90.5 (11.2)
Week 1	–4.3	p=0.942	–6.6	p=0.059	–4.2
Week 2	–8.6	p=0.062	–10.0[a]	p=0.015	–5.8
Week 3	–10.6[a,b]	p=0.023	–11.5[a]	p=0.012	–6.8
Week 4	–12.0[c,d]	p=0.006	–12.3[a]	p=0.012	–7.1

N=number of patients; ILO=iloperidone; ZIP=ziprasidone

[a] p<0.05 (2-tailed) compared with placebo based on MMRM analysis using baseline as covariate.

[b] p<0.05 (2-tailed) compared with placebo based on MMRM analysis using the randomization test method (1000 iterations). The randomization test method was only applied to the iloperidone vs. placebo comparison.

[c] p<0.01 (2-tailed) compared with placebo based on MMRM analysis using baseline as covariate.

[d] p<0.01 (2-tailed) compared with placebo based on MMRM analysis using the randomization test method (1000 iterations).

Note: Change is calculated as post-baseline minus baseline value, where negative change reflects improvement and positive change reflects worsening on the scale.

Source: VP-VYV-683-3101 CSR Post-text Table 9.2.1-2a

In conclusion, the Applicant has defined the onset window to 2-3 weeks and believe the delayed onset is no longer an issue in the context of the modified indication that the Applicant is seeking. A delay in onset may be acceptable to patients who have limited treatment options due to tolerability issues. According to the Applicant, the delay in onset no longer imposes any increased risk to the patient since titration will be monitored by a physician. The patient's schizophrenia symptoms can therefore be monitored and treated acutely by the physician and any delay in efficacy can be addressed by adjusting the monitoring period or fast hospitalization if the patient needs further stabilization. Therefore, the Applicant recommends Fanaptum only as a second line option for schizophrenia with acute symptoms or for patients already stabilized on other medications.

Long Term Maintenance - REPRIEVE Study 2301

Study 2301 measured time to relapse or impending relapse after being stabilized on iloperidone for 12 weeks. Based on a specific recommendation by the CHMP, this maintenance study was conducted by Novartis (ILO522D2301) according to a randomized placebo withdrawal design. Study subjects were adults with schizophrenia initially treated with open-label iloperidone 12 mg/day given as 6 mg BID and then stabilized for a further 14-24 weeks with a flexible-dose iloperidone regimen (range between 8-24 mg/day daily dose given BID) as per investigator. The average dose was 13mg/day during stabilization. Subjects who remained clinically stable for at least 12 weeks entered the relapse prevention phase and were randomized. A stabilization time of 12 weeks is a sufficient time for symptom stabilization and helps ensure patients are not simply "withdrawing" from the drug or still in a sub-episodic state. Time to relapse was 139 days for the iloperidone treated patients vs. 71 days for the placebo treated patients. The long time to relapse in the placebo arm also demonstrates that this was not a "withdrawal" effect. Rate of Relapse was 20.4 % for the iloperidone treated patients vs. 63.4% for the placebo treated patients. Iloperidone was superior to placebo in preventing and delaying relapse in schizophrenia patients.

In study 2301, approximately 50% of patients were stabilized on iloperidone and points to a significant of proportion of patients that can be treated with Fanaptum. Iloperidone was shown to be superior to placebo in preventing and delaying relapse in schizophrenia patients. The Applicant considers these strong results for the maintenance effect of iloperidone.

The Applicant agrees with the CHMP that stabilization before withdrawal enriches the study population with patients who are more amenable to stabilization and efficacy with iloperidone. However, this is the standard way to assess long term maintenance on antipsychotics. Moreover, 50% of the 629 patients enrolled into the REPRIEVE study stabilized on iloperidone and continued into the randomized withdrawal phase. This percentage is consistent with other antipychotics rate of stabilization and can therefore be extrapolated to the general schizophrenia population. Patients enrolled in study 2301 were drawn from the general schizophrenia patient population and not a "select group of patients". The inclusion criteria included patients having a prior diagnosis of schizophrenia and in need of ongoing psychiatric treatment. Patients also must have had a documented reason why a change in treatment was warranted.

A 50% success rate is consistent with the stabilization phase of other studies (Abilify, Latuda, etc.) This study identified a large proportion of the patient population that can be stabilized on iloperidone and who are seeking to change treatment. In conclusion, the Applicant believes that study 2301 shows that iloperidone is an effective treatment for a large portion of patients with schizophrenia and that it significantly delays and prevents relapse during the maintenance phase of schizophrenia.

A patient population that can benefit by Fanaptum and Company's Updated Risk Benefit Assessment

The Applicant now highlights a patient population for the CHMP that would benefit from Fanaptum. They believe a patient population is now more clearly identified with their newly modified indication. They recommend to treat:

- Schizophrenia patients who are stabilized and are having efficacy or tolerability issues with their current treatment and are willing to switch their medication.
- Patients who are in an acute schizophrenia episode and unable to be fully stabilized on another antipsychotic because of tolerability issues.

Taking into account the CHMP's safety and efficacy concerns for Fanaptum in an acute schizophrenia setting, the Applicant has modified Fanaptum's indication as a second line treatment option in schizophrenia.

The Applicant says that in the treatment of schizophrenia, it is well established that not every patient responds to each drug. This fact is exactly the reason why new options are needed and continue to be developed. Even if iloperidone was effective in fewer patients than other antipsychotics that would not make it at the individual level a less potent agent. In a hypothetical clinical trial if 40% responded to agent 1 and 20% responded to agent 2 that does not mean that agent 2 is less effective among the 20% of people who responded. In this case, agent 2 is predicted to be fully effective in 20% of the patients and still a useful drug. It is noteworthy that the differences in efficacy between antipsychotics on the market in the real world are very small (the CATIE study, the CUTLASS study). While iloperidone has been shown to be effective in treating patients with acute exacerbation, it is also true that given the availability of other agents, other drugs should be tried first, especially those that may not require titration. Patients will undergo titration of Fanaptum under a physicians care (an inpatient or outpatient setting), where they can be monitored with ECGs at baseline and after titration completion. Daily and weekly monitoring by a physician will mitigate the concerns of delay in efficacy onset due to titration.

Vanda has taken CHMP's feedback and concerns into consideration and made substantial modifications to the proposed indication and treatment paradigm, and believes that with the changes outlined herein, iloperidone demonstrates a compelling positive risk-benefit profile for an identifiable set of patients for the following reasons.

Despite the availability of several antipsychotics, schizophrenia treatment remains plagued by incomplete efficacy, high antipsychotic switch rates, substantial disease relapse, significant side-effect burden, and a 10% suicide risk. Since treatment adherence is largely driven by drug side effect tolerability, and atypical antipsychotics differ in their side-effect spectrum, patients primarily seek drugs that are long-term tolerable as well as effective for them. The overall data show that while there are a number of antipsychotics on the market, the individual tolerability is quite specific and some patients fail to find long-term tolerable and effective medications. This data indicates that there is still a compelling need for additional treatment options in schizophrenia.

Particularly troubling to patients are the range of motor side effects due to the dopamine antagonism of available treatments. Iloperidone has demonstrated, in virtually all studies, an overall superior motor side effect profile, particularly for akathisia. Akathisia, a common motor side effect of a number of antipsychotics (20% in some studies), is an extremely distressing condition causing restlessness, persistent and sometimes intractable involuntary movement, which is so upsetting to patients as to be an independent suicide risk. These findings support the notion that there is currently an unmet need for antipsychotics with low akathisia rates.

<u>Fanaptum's Benefits</u>

1. Iloperidone efficacy, evaluated while taking into consideration the titration period, is largely comparable to other members of the atypical antipsychotic class in both magnitude and timing, with strong evidence for efficacy in long-term relapse prevention. Taken in their totality, both short term and long term studies show that Fanaptum is a therapeutically meaningful agent for the treatment of schizophrenia. The Applicant believes this is a significant benefit of iloperidone treatment.

2. Iloperidone has a placebo-like akathisia rate and can represent a critical treatment option for patients who experience intolerable akathisia while taking other antipsyhotics. The Applicant believes that this represents a marked and therapeutically very relevant benefit on the side of iloperidone.

3. Iloperidone demonstrates a favorable side effect profile on several additional key measures, namely low to no extrapyramidal symptoms, mild sedation, mild weight gain, no substantial lipid elevations, and no prolactin elevation. The Applicant believes these are additional strong benefits of the proposed use of iloperidone.

4. Iloperidone benefits are supported by a large post-marketing experience spanning the year 2010 until the present, the USA, Mexico and Israel territories, and including over 70,000 patient-years. The considerable post-marketing period has not uncovered any new major safety or efficacy concerns. The Applicant believes this represents a very strong statement supporting the benefit of iloperidone treatment.

Fanaptum's Risk Mitigation Strategy

Iloperidone, like many other drugs, has a non-zero risk profile, particularly related to its ability to prolong the QT interval. This is a legitimate concern for any medication. Vanda has taken CHMP feedback on this matter and has proposed the following concrete measures to address this risk:

• Recommendation of CYP2D6 genotyping to identify patients who can be switched to iloperidone

• Starting iloperidone in CYP2D6 extensive metabolizers in a setting where ECG/QTc can be monitored at Cmax until reaching at least 12mg/day

• Increasing the dose beyond 12mg/day only with concomitant ECG/QTc monitoring

• Not recommending iloperidone as a first line drug for the treatment of acute schizophrenia

• Contraindicating iloperidone in poor CYP2D6 metabolizers

• Contraindicating iloperidone in patients who have known existing prolongation of cardiac conduction intervals, particularly QTc, patients with significant electrolyte disturbances or underlying cardiac diseases such as congestive heart failure

• Contraindicating co-administration with any QT-prolonging drugs

• Contraindicating co-administration with potent CYP2D6 inhibitors (regardless of their QT prolonging effects)

• Contraindicating co-administration with potent CYP3A4 inhibitors (regardless of their QT prolonging effects)

• Contraindicating Fanaptum in males with QTc >450 msec and females with > 470 msec

• Discontinuing Fanaptum if an QTc interval > 500 msec is observed

• Considering lower dose or discontinuing Fanaptum in individuals who are found to have KCNQ1 single nucleotide polymorphism (rs2283153) genotype G/G

Taken with the available data, Vanda believes that the proposed iloperidone utilization changes designed to address CHMP concern now represent a strongly positive risk-benefit analysis for iloperidone, and that Fanaptum should be granted marketing authorization for those reasons.

The Applicant also introduced the possibility to lower the threshold for QT at baseline for the contraindication.

Highlights from the RMP

In addition to the Applicant's updated indication and treatment algorithm, their risk management plan further ensures the safety of schizophrenia patients and can increase Fanaptum's positive benefit/risk ratio.

• Educational material for healthcare professionals to address the risk(s) of QT prolongation especially in patients who are poor metabolizers of CYP2D6 and also address weight gain and diabetes mellitus.

• Educational material for patients to address the risk of QT prolongation especially in patients who are poor metabolizers of CYP2D6

• Educational material for patients to address the risks of weight gain and diabetes mellitus.

• A Post-authorisation Safety Cohort Study to further investigate iloperidone (Fanaptum) induced weight gain, orthostatic hypotension and QT prolongation-related cardiac arrhythmias/sudden death and to evaluate the adherence to the prescription requirements in real life practice for schizophrenic patients.

• Determine the proportion of prescribers who received the DHCP and Educational materials

• Determine the extent of genotyping prior to initiating iloperidone therapy.

• Assess dosing practices when iloperidone is prescribed in normal clinical practice.

• Treatment algorithm field survey that measures adherence to prescribing information and adherence to treatment algorithm

Following a request from the applicant at the time of the re-examination, the CHMP convened an Ad Hoc expert Group inviting the experts to provide their views on the CHMP grounds for refusal, taking into account the applicant's response.

The applicant presented in front of the experts and of the CHMP in an Oral Explanation.

Report from the Ad-hoc Experts Group

1. The applicant has proposed a risk minimisation measures strategy including the following measures.

a. CYP2D6 genotyping before starting iloperidone treatment

b. Contraindication in CYP2D6 poor metabolizers

c. Contraindication in patients at risk of QT prolongation and cardiac arrhythmia, and congenital QT prolongation

d. Initiation of iloperidone treatment in clinical settings where the patient can be monitored by ECG taken at Tmax on every day of the titration period (minimum four days), and weekly thereafter for the first month of treatment.

e. Sequential monitoring with ECG with dose increase and as appropriate

f. Contraindication for patients on strong CYP2D6 inhibitors

g. Dose adjustments for patients on CYP3A4 inhibitors

What is the experts' view on the adequacy of these measures to appropriately address in clinical practice the risks identified?

The experts confirmed the view that Fanaptum can prolong the QT interval, and has the potential to induce events such as Torsade de Pointes. In this context the experts enquired the Applicant about the

number of sudden deaths reported from the clinical program, which according to their experience constitute a very high number of cases (relative to the total number of deaths cases and number of suicides). The magnitude of the risk of clinically meaningful events associated with QT prolongation is difficult to estimate precisely, as the experts expressed reservations about the comparability of the populations referred to by the Applicant in the calculations proposed.

After evaluating the baseline parameters of the population enrolled, the experts noted that the data from the thorough QT study does not seem suited to inform the effect on a high-risk population as it represents a population with a relatively "short" QT interval at baseline. According to the experts a QT study in patients with a longer baseline QT interval within normality ranges would better inform the effect of the product on QT prolongation.

The experts reflected that the causal chain linking the exposure to Iloperidone to events such as Torsade de Pointes is complex and includes some unknown or stochastic elements which by definition would be of very difficult control in any risk minimization plan to be implemented in the clinical setting. In consideration of this and of the available data, the experts concluded by majority that it is not possible to design a set of risk minimization measures that would appropriately address the risks identified and that the measures proposed would end up providing a false reassurance.

One of the experts expressed the view that the proposed measures – if duly implemented and intensified in some regards (for example regarding the periodicity of the ECG monitoring and its repetition in case potentially interacting medicines are co-administered) – would in theory address the risks, but he shared the view that the implementation in clinical practice would be subject to the effects of variability at different levels. As an example, the experts mentioned that while the recommendation would be to perform the ECG at Tmax, this could be missed due to either the variability of this parameter or to practical issues (for example, the availability of a suitably trained cardiologist).

2. For the re-examination, the applicant has proposed a second line indication, with the arguments focusing in particular on patients who do not tolerate other second generation antipsychotics because of EPS, especially akathisia. However the SGA active comparators in the clinical studies (risperidone and ziprasidone) are both associated with a relatively high incidence of EPS in comparison with some other SGAs. The experts are asked to comment on whether a patient population exists that is likely to tolerate iloperidone better than other available SGAs that have a relatively low incidence of EPS.

The experts observed that – due to the pattern of usage of antipsychotics in routine clinical settings – the definition of a "second line" indication would not be easily interpretable in absence of robust data that identify reliable specifiers, such as predictors of response or moderators of effect. In particular, the experts reported that it is common that the first antipsychotic given to a patient is discontinued for different reasons in a relatively short timeframe, and that for these patients a wide range of alternative options already exists.

The experts also noted that the papers by Citrome L (2017) – referenced as sources of indirect evidence of favorable tolerability and comparable efficacy profile – do not fulfil the methodological standards of systematic reviews (for instance, comprehensive search strategy, transparent and replicable inclusion criteria),, and this limits the reliability of the conclusions that can be drawn from them.

In consideration of the data presented and of a meta-analysis by Leucht et al (2017), the experts expressed the view that Iloperidone has a modest efficacy, in the lower end of the spectrum of the available Second Generation Antipsychotics, and with a low but not uniquely low propensity to cause EPS in general. Moreover, the risk of weight gain is significantly increased in patients treated with iloperidone, but the applicant did not present such data.

It has been acknowledged that the methodology employed in Leucht et al (2017) is not informative regarding the propensity to cause akathisia. The important clinical significance of akathisia has also been acknowledged. It is possible that patients discontinuing another treatment due to akathisia might benefit from the tolerability profile of Iloperidone. However, there is no convincing demonstration of a comparatively lower incidence of akathisia with Iloperidone as compared to other antipsychotics.

In view of all the above considerations, the experts could not clearly specify criteria that would identify a group of patients that is likely to tolerate Iloperidone better than other available Second Generation Antipsychotics. Hence, also in consideration of the limited efficacy, the experts could not clearly identify a suitable population for a definition of a therapeutic indication for Iloperidone.

Of note, the patients representatives agreed with this view and specified that the risks connected with the use of Iloperidone are not outweighed by the fulfilling of any unmet need (for example, by a demonstrated superior activity on cognitive or negative symptoms).

Overall conclusion on grounds for re-examination

The CHMP assessed all the detailed grounds for re-examination and argumentations presented by the Applicant and considered the views of the Ad Hoc Expert Group.

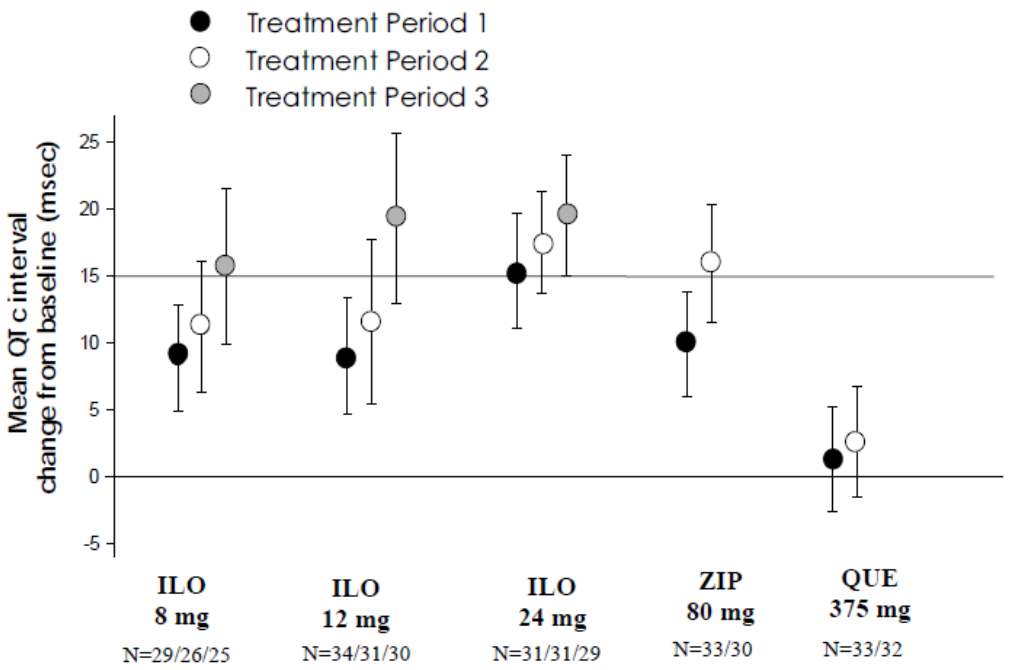
Unmet need in schizophrenia treatment

The persistence of unmet medical needs in the treatment of patients with Schizophrenia is acknowledged. Moreover, the CHMP agrees in considering Akathisia a clinically significant condition and an adverse event that limits the use of some available antipsychotics.

Ground #1

A calculations of the hERG IC50/free Cmax ratio for iloperidone and its metabolite P88 has been developed by taking values from studies 008167, ILO-522-2328 and XS-0531. This analysis has been discussed in a paper by Redfern et al (2003) which suggests that a margin of 30-fold between free therapeutic plasma concentration and hERG IC50 appears to be a line of discrimination between drugs that are associated with Torsade de Pointes and those that are not. This paper also clearly highlights a number of exceptions, where the ratio for a drug is more than 30-fold and the drug is considered to be torsadogenic and vice versa. Although these calculations are considered useful, it should be noted that the values taken for Cmax (ILO522-2328) were from a study in otherwise healthy patients diagnosed with schizophrenia or schizoaffective disorder, and it is possible that concomitant medications may influence the extent of plasma protein binding and therefore may alter the amount of free drug in plasma and therefore would significantly reduce this 30-fold margin. This has not been considered by the applicant in this response and much of the argumentation is similar to that initially assessed during the original procedure.

The thorough QTc study 2328 is considered to show substantial QT prolongation. Patients were randomly assigned to receive iloperidone (ILO) 8mg BID, ILO 12mg BID (the maximum recommended therapeutic dose), ILO 24 mg QD, ziprasidone 80 mg BID (positive control) or quetiapine 375 mg BID (negative control) in the absence (period 1) and presence of single (period 2) and dual (2D6 & 3A4 – period 3) metabolic inhibition.



ILO=iloperidone; ZIP=ziprasidone; QUE=quetiapine
P1=Period 1, P2=Period 2, P3=Period 3
Note: * T_{MAX} = estimated time of maximum concentration (ILO=2-4 hours post-dose; ZIP=5-7 hours post-dose; QUET= 1-2.5 hours post-dose)
Source: Figure 9.2-1

The fact that no subjects in this study experienced a QT or QTc value of greater than 500 msec is not necessarily reassuring as this is a group of subjects with no risk factors and a normal QT interval at baseline, and the number of subjects in the trial was not large (about 30 per group). The observation that seven subjects in the iloperidone treatment arms experienced a change in QTc value of > 60 msec at Tmax is evidence of a potential major safety issue.

It is also importantly noted, regarding the same study, that out of 94 patients exposed to Iloperidone at different doses without metabolic inhibition (i.e. in Treatment Period 1) in the Secondary QTc population 43 and 2 patients respectively developed a prolongation of the QTcF of more than 30 and 60 msec.

Table 9-3 Number (%) of patients with QTc increase from baseline to steady state at T_{MAX}* of ≥ 30 and 60 msec during Treatment Periods 1, 2, and 3 (Secondary QTc population)

	ILO 8 mg b.i.d.		ILO 12 mg b.i.d.		ILO 24 mg q.d.		ZIP 80 mg b.i.d.		QUET 375 mg b.i.d.	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Treatment Period 1										
Increase ≥ 30 msec										
Fridericia	29	9 (31)	34	15 (44)	31	19 (61)	33	17 (52)	33	4 (12)
Baseline	29	9 (31)	34	15 (44)	31	19 (61)	33	14 (42)	33	5 (15)
FDA	29	11 (38)	34	15 (44)	31	21 (68)	33	15 (45)	33	7 (21)
Bazett	29	21 (72)	34	21 (62)	31	26 (84)	33	20 (61)	33	18 (55)
Increase ≥ 60 msec										
Fridericia	29	1 (3)	34	0 (0)	31	1 (3)	33	0 (0)	33	0 (0)
Baseline	29	1 (3)	34	0 (0)	31	1 (3)	33	0 (0)	33	0 (0)
FDA	29	1 (3)	34	1 (3)	31	1 (3)	33	0 (0)	33	0 (0)
Bazett	29	1 (3)	34	3 (9)	31	4 (13)	33	5 (15)	33	1 (3)

Although the risk cannot be precisely quantified, QT prolongation of this magnitude is considered, according to conventional cardiological and regulatory thinking, to represent a significant hazard.

The increases of Cmax up to 2.3 fold observed with metabolic inhibition are not insignificant and importantly this is a mean value; it does not describe the extent to which some individuals might show a much greater increase in iloperidone Cmax in the presence of strong CYP3A4 and CYP2D6 inhibitors. This will depend on the activity of the minor metabolic pathways for iloperidone, which could very well be highly variable. In the context of the risk assessment for drug induced TdP the population mean effect is less relevant than the worst case scenario. No data are available to establish the likely effect on drug levels in patients with low activity of the minor metabolic pathways for Iloperidone exposed to mild CYP3A4 and CYP2D6 inhibitors.

The available data and the lack of interchangeability (and to some extent comparability) between the populations compared does not allow to exclude, confirm or quantify an excess cardiac mortality in the clinical development program. It is also difficult to conclude with certainty on the causality of the deaths which occurred in the development program in iloperidone treated patients that appeared to be of greatest concern in the context of QT prolongation (attributed to arrhythmia, sudden cardiac arrest and sudden death). It is important to note that clinical trials have inclusion / exclusion criteria and screening procedures that may exclude patients at risk more effectively than would occur in routine clinical practice. Also, trial investigators may pay greater attention to QT / drug interactions warnings than might be the case in clinical practice. The magnitude of this safety issue could therefore have been substantially underestimated.

Similarly, it seems impossible to estimate the extent of under-reporting of fatal outcomes in association with iloperidone. Post-marketing spontaneous report data are not considered to provide substantial reassurance regarding cardiac safety. There are various reasons why very substantial underreporting of deaths in relation to iloperidone might be expected. Sudden cardiac death in general cannot definitively be shown to be a result of iatrogenic QT prolongation and ventricular arrhythmia as there is no post mortem marker. Even where there is suspicion that this is a likely cause of death, a possible causal association with treatment might not be reported as iloperidone is well known to prolong the QT interval. Reporting of torsades de pointes in patients taking iloperidone seems more likely than reporting of sudden death but the degree to which the lack of reports might be reassuring cannot be evaluated as there is no information on the numbers of other known treatment related AEs that might be expected to be collected

in spontaneous reporting. The calculations proposed are hence not considered useful or reassuring.

It is acknowledged that for a niche product intended for use in a small number of patients the proposed risk minimisation measures would seem to be feasible in some clinical settings in the EU but probably not all. However, the ability of the proposed measures to appropriately address the risks is questioned in presence of known and unknown sources of variability. Some examples of this can be provided but a comprehensive list cannot by definition be formulated:

- While the recommendation would be to perform the ECG at Tmax, this could be missed due to intrinsic or extrinsic factors.
- The increase in exposure with non-contraindicated inhibitors of Iloperidone's metabolism might be subject to a significant variability in presence of a small safety margin.

Similarly, the proposal to lower the threshold for contraindicating Fanaptum based on QT at baseline cannot be accepted due to the within-subject variability of this measurement in the population concerned.

Regarding the above two scenarios proposed by the applicant as scenarios where Fanaptum may be a useful treatment:

1) Schizophrenia patients who are stabilized, but because of poor tolerability or suboptimal efficacy need to switch to another antipsychotic medication.

> It is agreed that some patients do need to switch to another antipsychotic medication because of poor tolerability or suboptimal efficacy. However there are no data to indicate that a population of patients exists who will respond more favourably to a switch to iloperidone than to a switch to an appropriate alternative second generation antipsychotic. The applicant emphasises the lower incidence of EPS, in particular akathisia, in patients treated with iloperidone compared with those treated with the active comparators risperidone and ziprasidone. However the latter two drugs are known to cause more EPS (including akathisia) than some other second-generation antipsychotics. For example the European First Episode Schizophrenia Trial showed the following rates of SGA induced acute akathisia: amisulpride (200–800 mg, 16%), olanzapine (5–20 mg, 10%), quetiapine (200–750 mg, 13%) and ziprasidone (40–160 mg, 28%). Kane et al reported that risperidone, ziprasidone and aripiprazole possess a higher risk than olanzapine, whereas quetiapine and clozapine present the lowest risk, although explicit comparative evaluation is lacking (Kane JM, Fleischhacker WW, Hansen L, Perlis R, Pikalov A, Assunção-Talbott S. Akathisia: an updated review focusing on second-generation antipsychotics. J Clin Psychiatry 2009 ; 70: 627– 43). So in the scenarios described above, with lack of tolerability due to occurrence of EPS / akathisia, the natural therapeutic decision would be to switch to one of the aforementioned lower EPS risk agents such as quetiapine. Importantly, there are no data comparing either efficacy or tolerability of iloperidone versus other SGAs that cause less problems with EPS than risperidone or ziprasidone. The comparison proposed referencing to Citrome (2017) cannot be used to draw any reliable conclusion as the methodology does not fulfil the methodological standards of systematic reviews (for instance, comprehensive search strategy, transparent and replicable inclusion criteria). There is no basis for a claim that iloperidone addresses a clinical need in patients with troublesome EPS / akathisia that could not be met at least as well by for example quetiapine or olanzapine.

2) Schizophrenia patients in acute distress and unable to be stabilized on another antipsychotic medication for tolerability reasons.

Again there are no data to suggest that iloperidone may have a tolerability advantage over existing and safer treatment options. Furthermore the slow onset of action of iloperidone makes it generally less suitable for the acute situation described.

Ground #2

It is agreed that 3101 is a positive trial showing evidence of efficacy that seems broadly comparable to that of ziprasidone after 4 weeks. The known slower onset of efficacy in comparison with other SGAs can be seen here. The difference from placebo of 5 points on the PANSS is fairly modest in comparison with pivotal efficacy trials for some other SGAs but this is not evidence of inferiority of iloperidone.

As noted in the original assessment Studies 3000, 3004 and 3005 were collectively supportive of efficacy that can be considered to be proven but of modest magnitude in comparison with results achieved for other SGAs. It is important to consider again the results of these trials.

Study 3004 provides data on the efficacy of iloperidone in comparison with both placebo and the active comparator risperidone. Differences from placebo on the PANSS for the three treatment arms were 3.8 (Ilo 4-8 mg/day), 4.7 (Ilo 10-16 mg/day) and 7.8 (risperidone 4-8 mg/day). This trial is discussed further below.

In study 3000 the primary endpoint (PANSS-T score at Week 6 for iloperidone, average of the 8 mg/d and 12 mg/d dose groups) compared to placebo was not met although there was a trend of improvement. In contrast the active comparator haloperidol showed clear superiority to placebo. The main results by week of treatment are presented in the following table:

PANSS-T adjusted mean change from baseline by week, LOCF analysis (study 3000)

Timepoint	ILO 4 mg/d n=113		ILO 8 mg/d n=114		ILO 12 mg/d n=115		HAL 15 mg/d n=114		Placebo n=117
Baseline (SD)	95.0 (15.3)		95.7 (15.9)		94.6 (14.8)		96.1 (15.6)		95.0 (17.0)
Week 1	-3.1	p=0.710	-4.0	p=0.928	-4.7	p=0.646	-6.8	p=0.120	-3.8
Week 2	-4.3	p=0.936	-6.2	p=0.335	-6.0	p=0.387	**-12.1***	**p<0.001**	-4.1
Week 3	-6.9	p=0.259	-7.1	p=0.238	-8.2	p=0.098	**-12.7***	**p<0.001**	-4.3
Week 4#	-7.8	p=0.124	-6.7	p=0.277	**-10.0***	**p=0.015**	**-13.5***	**p<0.001**	-3.9
Week 5	-8.5	p=0.146	-6.6	p=0.466	-9.5	p=0.065	**-13.3***	**p<0.001**	-4.8
Week 6	-9.0	p=0.097	-7.8	p=0.227	**-9.9***	**p=0.047**	**-13.9***	**p<0.001**	-4.6

N=number of patients; ILO=iloperidone; HAL=haloperidol
* p<0.05 (two-tailed) compared with placebo; based on t test using ANCOVA model.
# p<0.05 for ILO (8 mg + 12 mg)/2 compared with placebo

Study 3005 also provided data in comparison with both placebo and the active comparator risperidone, and (unlike study 3004) included the maximum proposed dose of iloperidone 24mg/day. The primary efficacy variable was change from baseline to Day 42 in the BPRS score for the ILO 12-16 mg/d group, (LOCF). From Week 3 through Week 5 for the ILO 12-16 mg/d group, the adjusted mean change from baseline was nominally statistically superior to placebo. Statistically significant improvement was lost at Week 6, the protocol specified endpoint. The main results by week of treatment are presented in the table. Again risperidone appeared to show greater efficacy than iloperidone although the trial was not powered for a formal comparison of the efficacy of iloperidone versus risperidone.

BPRS adjusted mean change from baseline by week, LOCF analysis (Study 3005)

Timepoint	ILO 12-16 mg/d n=230		ILO 20-24 mg/d n=141		RIS 6-8 mg/d n=148		Placebo n=152
Baseline (SD)	54.4 (7.3)		54.9 (8.0)		55.0 (8.8)		55.4 (8.2)
Week 1	-2.6	p=0.727	-3.2	p=0.717	**-4.9***	**p=0.013**	-2.8
Week 2	-4.9	p=0.390	-5.5	p=0.165	**-8.4***	**p<0.001**	-4.0
Week 3	**-6.9***	**p=0.012**	**-6.7***	**p=0.031**	**-9.8***	**p<0.001**	-4.1
Week 4	**-7.5***	**p=0.035**	**-8.1***	**p=0.022**	**-10.9***	**p<0.001**	-5.1
Week 5	**-7.7***	**p=0.037**	**-8.6***	**p=0.012**	**-11.6***	**p<0.001**	-5.2
Week 6	-7.1	p=0.090	**-8.6***	**p=0.010**	**-11.5***	**p<0.001**	-5.0

N=number of patients; ILO=iloperidone; RIS=risperidone

*** p<0.05 (two-tailed) compared with placebo; based on t test using ANCOVA model.**

Study 3004 had a six week randomised treatment period. One might expect the two week titration for iloperidone and delayed onset to be no longer a major factor in the efficacy measures after a total of six weeks of treatment.

Based on the available evidence from study 3004 the likelihood is that ilpoperidone 10-16 mg/day is a little less efficacious than risperidone 4-8 mg/day. This conclusion is supported by the resiults of Study 3005, in which the estimated efficacy of iloperidone 20-24mg/day was numerically less than that of risperidone 6-8mg / day. Nevertheless it is not possible to conclude formally that the efficacy of iloperidone is inferior to that of risperidone, at optimal recommended doses.

The post-hoc analysis of trial 3005 proposed by the Applicant, lacking baseline predictors of compliance, does not seem to provide the most meaningful estimation of effect.

The Forest plots presented by the applicant are broadly supportive of the pivotal trial 3101 in terms of estimating the magnitude of the treatment effect to be about 5 points on the PANSS superior to placebo. This can be accepted as representing clinically relevant efficacy but is rather less than the 8-10 points superiority to placebo that has typically been seen with a number of currently approved SGAs. However these figures represent population means and are not necessarily predictive of the response that might be seen in different individual patients.

It is unfortunate that the data presented by the company in Table 11 have omitted the results for the risperidone and haloperidol active comparator groups, both of which appeared to be superior to iloperidone as previously noted.

As for the one discussed above, the indirect comparison by Citrome (2016), referenced by the Applicant, cannot be used to draw reliable conclusions due the same methodological limitations.

The acknowledged delayed onset of efficacy would not be considered in itself to be an impediment for approval of iloperidone. However it does inherently limit the clinical situations in which iloperidone might be considered, as it is less well suited for managing acute psychotic episodes.

It is agreed that long-term efficacy (maintenance of effect) was demonstrated in the randomised withdrawal study 2301. This was the conclusion in the original assessment.

Conclusion and Updated Risk Benefit Assessment

Considering all available non-clinical and clinical data (including the thorough QTc study, the overall clinical program and the cases of cardiac-related/sudden unexplained death in clinical trials and post-marketing), Iloperidone has a substantial and exposure-dependent arrhythmogenic potential. It is not considered that the risk minimization measures proposed would appropriately address the risk identified in this specific case. Hence, the safety of Iloperidone has not been sufficiently demonstrated.

Furthermore, Iloperidone has a modest efficacy. In addition, it has shown a delayed onset of action, which is a significant concern in the treatment of acute exacerbation of schizophrenia. Therefore, and taking into account the overall safety and efficacy profile of Iloperidone a patient population cannot be identified where the benefit of treatment is considered to outweigh the major safety concerns.

Based on the above, the risk-benefit balance of Iloperidone is considered negative.

5.1. Conclusions

The overall B/R of Fanaptum is negative.

6. Recommendations following re-examination

Based on the arguments of the applicant and all the supporting data on quality, safety and efficacy, the CHMP re-examined its initial opinion and in its final opinion concluded by consensus that the safety of Fanaptum in the treatment of schizophrenia in adults as a second line option is not sufficiently demonstrated and, therefore, recommends the refusal of the granting of the marketing authorisation for the above mentioned medicinal product.