26 February 2026
EMA/CHMP/117893/2026
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Iloperidone Vanda Pharmaceuticals

International non-proprietary name: Iloperidone

Procedure No. EMEA/H/C/006561/0000

Note

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

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List of abbreviations

ANCOVA	Analysis of covariance
ANOVA	analysis of variance
b.i.d. / BID	bis in diem/ twice-a-day
BAS	Barnes Akathisia Scale
BPRS	18-item PANSS-derived Brief Psychiatric Rating Scale
CDS/CDSS	Calgary Depression Scale for Schizophrenia
CGI-C	Clinical Global Impression of Change
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
Cmax	maximum concentration
CNTF	Ciliary neurotropic factor
CSF	Cerebrospinal fluid
CSR	Clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	Cytochrome P450
DBRP	Double-blind relapse prevention
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECG	Electrocardiogram
EPS	Extrapyramidal symptoms
ESRS	Extrapyramidal Symptom Rating Scale
FAS	Full analysis set
HAL	Haloperidol
ICD	International Classification of Diseases
ILO	Iloperidone
ITT	Intent-to-treat
IVRS	interactive voice response system
LOCF	Last observation carried forward
MADRS	Montgomery-Asberg Depression Rating Scale
MCID	Minimal clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities Terminology
msec	Millisecond
OC	Observed cases
PANSS	Positive and Negative Syndrome Scale
PG	Pharmacogenetics
PPS	Per protocol set
q.d. / QD	Quaque die/once-a-day
QT	the QT interval of the ECG waveform
QTc	corrected QT value
QTcF	Fridericia-corrected QT value
RIS	Risperidone
SAP	Statistical analysis plan
SDS	Sheehan Disability Scale
SNP	single nucleotide polymorphism
SSD1	Steady-state day 1

SSD2	Steady-state day 2
SSD3	Steady-state day 3
SUMD	Scale to assess Unawareness of Mental Disorder
TdP	torsades de pointes
TEAE	Treatment emergent adverse event
T_{max}	Time at which maximum blood concentration is reached
YMRS	Young-Ziegler mania rating scale
ZIP	Ziprasidone

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Vanda Pharmaceuticals Netherlands B.V. submitted on 18 November 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Iloperidone Vanda Pharmaceuticals, 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 21 March 2024.

The applicant applied for the following indication:

Iloperidone is indicated for:

- Treatment of schizophrenia in adults.
- Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults.

1.2. Legal basis, dossier content

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 test(s) or study(ies).

1.3. Information on Paediatric requirements

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

1.4. Information relating to orphan market exclusivity

1.4.1. 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.

1.5. Applicant's request(s) for consideration

1.5.1. 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.

1.6. Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
25 March 1999	CPMP/775/99	Dr. Van Zwieten-Boot, Prof. Sampaio
21 September 2001	CPMP/2366/00	Prof. Sampaio, Dr. Jonsson

The Scientific advice pertained to the following clinical aspects:

- Phase 3 programme design, including study endpoints, dosing rationale, adequacy of data to support safety, and long-term efficacy data.
- Higher dose range, primary efficacy analysis, bioequivalence among formulations used in phase 3 clinical studies, bioavailability relative to an oral solution.

1.7. Steps taken for the assessment of the product

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

Rapporteur: Kristina Dunder Co-Rapporteur: Ewa Balkowiec Iskra

The application was received by the EMA on	18 November 2024
The procedure started on	27 December 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	17 March 2025
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	31 March 2025
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	25 April 2025
The applicant submitted the responses to the CHMP consolidated List of Questions on	17 July 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	25 August 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	4 September 2025
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	18 September 2025
The applicant submitted the responses to the CHMP List of Outstanding Issues on	14 October 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint	29 October 2025

Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	
The CHMP agreed on the consolidated second List of Questions to be sent to the applicant during the meeting on	13 November 2025
The applicant submitted the responses to the CHMP consolidated second List of Questions on	23 December 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the second List of Outstanding Issues to all CHMP and PRAC members on	14 January 2026
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	28 January 2026
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 Iloperidone Vanda Pharmaceuticals on	26 February 2026
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	26 February 2026

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The Applicant sought the following proposed indications for iloperidone:

- Treatment of schizophrenia in adults.
- Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults.

2.1.2. Epidemiology

The 12-month prevalence of schizophrenia in Europe is estimated to be 0.31%, and the lifetime prevalence is approximately 0.5%. Patients with schizophrenia have a 2.9-fold increased all-cause mortality and a 9.7-fold increased mortality by suicide compared to the general population. Use of any antipsychotic versus non-use is associated with a reduction of all-cause mortality in patients with schizophrenia.

The lifetime prevalence of bipolar I disorder is estimated to be 1% to 2% in both men and women in Europe, and the 12-month prevalence estimates for bipolar disorders (including type 1 and 2) are approximately 1% (range 0.5-1.1%) across European countries. Like schizophrenia, bipolar disorder is associated with increased mortality compared to the general population. The mortality gap appears to be widening over time.

The societal implications of both conditions are significant, both in terms of direct medical costs and in terms of indirect costs including productivity losses and caregiver burden.

2.1.3. Aetiology and pathogenesis

The aetiology of both schizophrenia and bipolar disorder is complex and not fully understood, but research suggests it results from a combination of genetic, environmental, and neurobiological factors. Both conditions have a strong genetic component, with heritability estimated at around 80%. However, no single gene is responsible; rather, multiple genetic variations contribute to increased risk.

Antipsychotic medications primarily work by modulating neurotransmitter activity in the brain, particularly dopamine and serotonin.

2.1.4. Clinical presentation

Schizophrenia is a progressive and recurring disorder characterized by multiple psychotic relapses and potential functional decline over time. The most common age of onset is in late adolescence/early adulthood. The onset can be either acute or insidious, with insidious onset often associated with poorer outcomes. About two-thirds of patients experience at least one relapse after their initial episode. Following each relapse, approximately 1 in 6 patients may not fully remit from the episode. Pharmacological treatment shortens the duration of psychotic episodes and lessens the risk of relapse. Schizophrenia often leads to impaired global functioning, even in patients considered to be in remission. While significant advances have been made over the last fifty years, the pharmacological treatments available are not curative and mainly target the positive symptoms. A significant unmet medical need remains.

The natural course of bipolar I disorder is characterized by recurrent episodes of mania and depression, with significant impacts on functioning over time. Bipolar I disorder is highly recurrent, and patients may experience manic, depressive, or mixed episodes. Full recovery without further episodes is rare, with recurrence and incomplete remission being the rule. Pharmacological treatment shortens the duration of manic/mixed/depressive episodes and lessens the risk of relapse. As in schizophrenia, the pharmacological treatments available are not curative. A significant unmet medical need remains.

Diagnostic criteria for both conditions are described in the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, fifth edition).

2.1.5. Management

For the treatment of schizophrenia, antipsychotic agents (dopamine receptor antagonists/partial agonists) are the standard of care, preferably combined with non-pharmacological treatment approaches. For the acute treatment of manic or mixed episodes lithium, antipsychotics and mood stabilisers are the standard of care.

There are several approved medicinal products for both conditions, and although national, European and other treatment guidelines exist, the treatment choice is largely left to the discretion of the individual prescriber. For schizophrenia, one of the newer "second generation" or "atypical" antipsychotics is usually recommended for first-episode patients, and clozapine is recommended for patients who have had an inadequate response to at least two other antipsychotic medications.

The most significant side effects of the available antipsychotics are weight gain, diabetes, dyslipidaemia, extrapyramidal symptoms, akathisia, prolactin elevation, sedation and QTc prolongation.

Although many treatment options exist, there is an unmet medical need as treatment discontinuation is very common in both schizophrenia and bipolar disorder, because of actual or perceived lack of effect, side effects and lack of insight in the nature of the disorder and the risk of relapse.

2.2. About the product

Pharmacotherapeutic group: psycholeptics; other antipsychotics; ATC code: N05AX14.

Iloperidone is a piperidinyl benzisoxazole derivative developed for treatment of schizophrenia in adults. The currently proposed indication also includes acute treatment of manic or mixed episodes associated with bipolar I disorder in adults. It acts as antagonist at dopaminergic, serotonergic and adrenergic receptors having affinity to dopaminergic D2 and D3 receptors, serotonergic 5-HT1a and 5-HT2a, and adrenergic α1 and α2c 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. The recommended target dose for CYP2D6 poor metabolisers and patients taking CYP2D6 or CYP3A4 inhibitors should not exceed 6 mg twice daily.

2.3. Type of Application and aspects on development

The clinical development of iloperidone was initiated by Hoechst Marion-Roussel (HMR) in 1990. HMR conducted 13 Phase 1 and 2 studies. In 1998, Novartis Pharmaceutical Corporation/Novartis Pharma AG (Novartis) licensed iloperidone and continued its clinical development program, conducting 19 Phase 1, 2 or 3 clinical studies.

In 2004, Vanda Pharmaceuticals Inc (Vanda) licensed iloperidone from Novartis and completed the schizophrenia clinical development program needed for registration in the US. In 2009, iloperidone was approved by the FDA for the acute treatment of schizophrenia in adults. In 2016, iloperidone was approved by the FDA for the maintenance treatment of schizophrenia in adult patients. In 2024, iloperidone was approved by the US FDA for acute treatment of manic or mixed episodes associated with bipolar I disorder in adult patients.

Vanda applied for marketing authorization in the EU in 2011 (Fanaptum EMEA/H/C/002371) for an indication in schizophrenia but decided to withdraw that application when it was clear from CHMP feedback that a long-term placebo-controlled relapse prevention study (maintenance withdrawal design) would be required. Following completion of the maintenance study, Vanda resubmitted an MAA in 2015 (Fanaptum EMEA/H/C/004149). The outcome of this resubmission was a refusal of marketing authorisation based on significant safety risks, efficacy uncertainties and overall negative benefit/risk.

Novartis received Scientific Advice from the CPMP in 1999 and 2000. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

In 1999, Novartis met with the CPMP to obtain alignment for the studies and study designs Novartis

planned to implement for the treatment of psychotic disorders. During this meeting, the CPMP provided Novartis the following advice: (1) Novartis' proposed development program seemed suitable to support the claim for the treatment of schizophrenia but not comprehensive enough to support the claim for the treatment of psychotic disorders, (2) recommended to exclude patients with schizoaffective disorder in their studies, and (3) recommended to Novartis to use time-to-relapse as the primary efficacy outcome measure in their planned 12-month (52-week), active controlled, non-inferiority studies comparing the long-term maintenance effect of iloperidone compared to haloperidol.

In 2001, Novartis met with the National Regulatory Authorities of England (MCA), France (AFSSAPS), Germany (BfArM), the Netherlands (MEB), and Sweden (MPA) to gauge which of these authorities would be willing to act as a Reference Member State if Novartis would use the Mutual Recognition procedure. At these meetings, France and Sweden expressed interest in reviewing the application. Sweden commented that the doses for the active comparators generally exceeded what is typically used in Europe in clinical practice. Both Sweden and Germany reminded Novartis that including patients with schizoaffective disorder in their studies deviated from the CPMP guidance.

To date, Vanda Pharmaceuticals has neither requested nor received any scientific advice from the CHMP or any National Regulatory Authorities beyond ones sought from Novartis.

2.4. Quality aspects

General comments on compliance with GMP

Active substance: Valid QP declarations are available. All active substance manufacturing sites are GMP compliant.

Finished product: For all sites involved in the manufacture, control and batch release of the finished product sufficient evidence of GMP compliance has been provided.

During the assessment, no specific issues to be addressed during a GMP inspection were identified.

2.4.1. Introduction

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

Other ingredients are: lactose monohydrate, crospovidone, hypromellose, microcrystalline cellulose, magnesium stearate and silica, colloidal anhydrous.

The product is available in full aluminium (polyamide/aluminium/PVC foil – aluminium lid) blisters placed into paperboard cards and sealed (dose titration cards) (treatment initiation pack) and high-density polyethylene (HDPE) bottles with child-resistant polypropylene closures containing an aluminium foil heat induction seal, and a silica gel desiccant (maintenance pack).

2.4.2. Active Substance

2.4.2.1. General information

The chemical name of iloperidone is 1-[4-[3-[4-(6-fluoro-1,2-benzoxazol-3-yl)-1-piperidinyl] propoxy]-3-methoxyphenyl] ethanone corresponding to the molecular formula $C_{24}H_{27}FN_2O_4$. It has a relative molecular mass of 426.28 and the following structure:

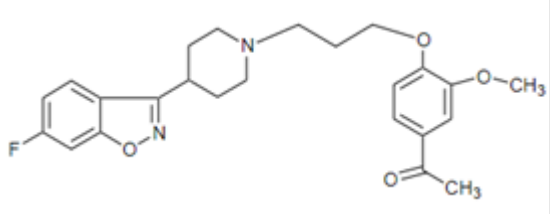


Figure 1: Active substance structure

The chemical structure of iloperidone was elucidated by a combination of NMR spectroscopy (1D-proton [1H], 1D-carbon [13C], gradient COSY, gradient HSQC, and gradient HMBC), mass spectrometry, FT-IR spectroscopy, UV spectroscopy, and elemental analysis. The solid-state properties of the active substance were measured by DSC, FT-IR and XRPD.

The active substance is a white to off-white crystalline powder with a melting range of 120.5-123.5°C. It is highly permeable and soluble in organic solvents such as acetonitrile and methanol. The aqueous solubility of iloperidone is pH dependant, being moderately soluble in acidic aqueous environments, and sparingly soluble in basic aqueous environments.

Iloperidone has a non-chiral molecular structure.

2.4.2.2. Manufacture, characterisation and process controls

The active substance is manufactured at two manufacturing sites and a third manufacturing site performs an additional milling step on the active substance from both these sources.

The initial GMP documentation from both active substance manufacturing sites was incomplete since manufacturing sites performing the critical micronisation step were not covered. Therefore, the CHMP requested a major objection (MO) to address the missing GMP information. The applicant has appropriately addressed this MO in their responses providing evidence of appropriate GMP standards for all manufacturing sites.

For one manufacturer full details of manufacture are submitted by the applicant as part of the application.

Iloperidone is synthesised in six main steps using four commercially available, well defined starting materials with acceptable specifications. A MO was raised initially since incomplete information was given on the starting materials manufacturing sites, and also, the relevant synthetic schemes and the justification of the starting materials was insufficiently addressed. The applicant has addressed this by providing: the names and addresses of the starting materials manufacturers, the schemes for the synthetic routes of the starting materials, the justifications for their selection in accordance with ICH Q11.

The manufacturing process of iloperidone is a convergent 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 to obtain the target particle size distribution.

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 active substances. The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. The quality of the active substance used in the various phases of the development is comparable with that produced by the proposed commercial process.

The active substance packaging complies with Commission Regulation EC 10/2011, as amended.

A similar synthetic process using the same starting materials is proposed in the ASMF from the second manufacturer.

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory. A MO was raised in the first round since the selected starting materials were insufficiently justified as per ICHQ11 principles. The applicant resolved the MO by providing sufficient justification which outlined among other aspects that the proposed starting materials are commercially available and demonstrated that the requirements of ICHQ11 are met.

Iloperidone is synthesised in seven main steps using commercially available well defined starting materials with acceptable specifications. It is a convergent synthesis with two branches to obtain the final intermediates which are then coupled in the last step of the synthesis to form crude iloperidone. The two final intermediates are isolated. Crude iloperidone is subsequently crystallised and milled to the target particle size distribution.

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 active substances. The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. The synthetic route was practically unchanged throughout the development process, except for an equipment change which initiated an overall process revalidation. This change did not have a significant impact on the quality of the product. The quality of the active substance used in the various phases of the development is comparable with that produced by the proposed commercial process.

The active substance packaging complies with Commission Regulation (EU) 10/2011, as amended.

Regarding the ASMF, an outstanding other concern (OC) is raised since the applicant’s part of the ASMF does not cover all sub-sections submitted in sequence 0009. A complete version of the applicant’s part should be presented in the closing sequence by the finished product manufacturer.

2.4.2.3. Specification

The active substance specification from the applicant Vanda includes tests for: appearance (visual), identity (FT-IR), melting point (Ph. Eur.), purity (DSC), loss on drying (TGA, Ph. Eur.), related substances (HPLC, GC) , elemental impurities (ICP-OES), residual solvent n-butyl acetate (GC), assay (HPLC, potentiometric titration), loss on drying (Ph. Eur.), particle size distribution (laser diffraction),

polymorphic form (XRD), sulphated ash (Ph. Eur.), appearance of solution (Ph. Eur.), colour of solution (Ph. Eur.), microbial limits (Ph. Eur.), bacterial endotoxins (Ph. Eur.), residual solvent (GC-FID).

The active substance specification is appropriately justified. Tests and acceptance limits are performed in accordance with general compendial requirements and ICH Q6A, ICH Q3A, ICHQ3C & ICHM7 requirements.

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. A question was raised in the first round regarding the proposed limit of an impurity as it exceeded the ICH Q3A qualification threshold. The question was upgraded to a MO after receiving an inadequate response. Further reassurance in the next round was given that the proposed level is toxicologically qualified and the MO was resolved.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines, except for methods used for active substance from one manufacturer. A commitment is made that the updated method validation reports would be provided in July 2026. Satisfactory information regarding the reference standards used for identity, assay and impurities testing has been presented.

Batch analysis data from the applicant are provided. The results are within the specifications and consistent from batch to batch.

2.4.2.4. Stability

The stability batches from one manufacturer were stored for up to 60 months under long term storage conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to ICH guidelines. The following parameters were tested: appearance, identification by IR, identification by XRD, melting point, loss on drying, appearance of solution, colour of solution, assay, related substances, microbial limits and bacterial endotoxins. The analytical methods used were the same as for release and are stability indicating. All tested parameters were within the specifications, and no significant trends were noted.

Photostability testing following ICH guideline Q1B was performed on one batch. Results under stressed conditions (3 days at 100°C as bulk, in H2O, in 0.1N NaOH, in 0.1 N HCl, 10% H2O2 and photolytic stress) were also provided from a different batch. Mass balance and peak purity results confirm the control method for iloperidone drug substance is stability-indicating.

Based on the available data, a retest period of five years stored at or below 25 ± 2°C, in a tightly closed container to protect from moisture and light is proposed. Provided that the updated method validation reports are submitted by this manufacturer the proposed re-test period can be accepted.

Stability data from 3 commercial scale batches of active substance from the second manufacturer stored in the intended commercial package for up to 60 months under long term conditions (25ºC/60%RH) and for up to 6 months under accelerated conditions (40ºC/75% RH) according to the ICH guidelines were provided.

The following parameters were tested: appearance, identification, x-ray powder diffraction, loss on drying, assay, related substances, and microbial enumeration tests. The analytical methods used were the same as for release and are stability indicating.

All tested parameters were within the specifications, and no significant trends were noted.

Photostability testing was performed as part of forced degradation studies (acid/base hydrolysis, oxidation, heat, heat/humidity, photolytic stress) for the HPLC method validation on one batch.

The stability results indicate that the active substance is sufficiently stable and no stability differences are observed compared to the active substance from the other manufacturer. The stability results justify the proposed retest period of five years at 25 ± 2°C in the proposed container.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The proposed finished product is presented as white, round, flat, bevelled-edge immediate release tablets with the tablet strength debossed on the upper face and the company logo debossed on the lower face. The tablets contain 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg or 12 mg of iloperidone. 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 aim of 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.

The characteristics of the active substance that influence the finished product tablet performance have been adequately discussed, such as solubility, particle size, polymorphism and stability. The active substance is micronised to improve manufacturability of the finished product. The particle size and solid-state properties are suitably controlled in the active substance specification.

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 choice of the excipients is based on results from compatibility studies.

The finished product tablets are manufactured by a common process which consists of the following unit operations: blending, wet granulation, fluid bed drying, final blending, and compression.

The development of the dissolution method was performed using the whole range of tablet strengths and was based on the solubility properties of the active substance in different media across the physiological pH range. A medium was chosen where sink conditions were met for all tablet strengths and which exhibited a greater discriminating ability.

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

2.4.3.2. Manufacture of the product and process controls

The finished product is manufactured at one manufacturing site. Sufficient evidence of GMP compliance has been provided.

The manufacturing process consists of the following main steps: pre-blending, wet granulation, fluid-bed drying, milling, final blending, compression, and packaging. All steps except milling, tabletting and packaging are considered critical. The process is considered to be a non-standard manufacturing

process for 1 mg and 2 mg tablets due to the low active substance content (< 2% of composition). For the other tablet strengths, the manufacturing process is a standard process.

Major steps of the manufacturing process have been validated by several validation campaigns using a significant number of production scale batches covering all tablet strengths. 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.

2.4.3.3. Product specification

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

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

The initial risk assessment concerning the potential presence of nitrosamine impurities in the finished product was very brief without substantiating the risk from excipients and the resulting risk of nitrosamine impurities in the finished product from amine sources. Confirmatory test results excluded the presence of potential nitrosamines in the active substance manufacturing process from one manufacturer. Even though the manufacturing process for both active substance manufacturers is similar, different starting material manufacturers can produce starting materials with different risk level. Therefore, the CHMP raised a MO to request confirmatory test results from the second manufacturer and to provide a detailed risk assessment with consideration of all possible root causes for presence of nitrosamines listed in the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020), including confirmatory testing of the finished product.

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 impurity testing has been presented.

Batch analysis results are provided for a large number of batches including at commercial scale (used for clinical, registration stability and validation purposes) covering all tablet strengths and confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.4.3.4. Stability of the product

Stability data from a large number of finished product batches stored for up to 60 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The finished product batches were manufactured at a commercial manufacturer and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, identification, assay, dissolution, disintegration, hardness, loss on drying, related substances and microbial purity. The analytical procedures used were the same as the ones to be used for routine control, and are stability indicating.

The test results after 60 months under long-term and 6 months under accelerated conditions show that all parameters comply with the specifications and no significant changes have been observed.

Furthermore, the stability data from commercial scale process validation batches of 1, 2, 4, 6, 8, 10 and 12 mg tablets in HDPE bottles (14- and 60-count bottles) and 1, 2, 4, and 6 mg tablets in PA/Al/PVC/Al blisters from a commercial manufacturer have been provided. All batches have remained within their respective stability acceptance criteria after 36 months under long-term storage conditions and 6 months of stability studies at accelerated storage conditions and no significant changes have been observed.

In addition, all tablet strengths from a large number of batches (development and registration stability batches in the commercial packagings) were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Based on these studies, a special storage precaution - store in the original package in order to protect from moisture and light, was proposed. An in-use shelf life of 30 days has been claimed based on development data. In-use stability studies with repeated opening and closing of the container are required to establish an in-use shelf life according to guideline CPMP/QWP/2934/99, and if justified based on the EMA Q&A 'Claims for in-use shelf-life for solid oral dosage forms in multi-dose containers'. This was raised as an outstanding OC and the applicant has committed to perform an in-use stability study. In case of a future application, the applicant is recommended to address these points.

Based on available stability data, the proposed shelf-life of 3 years when stored in the original package in order to protect from moisture and light and keep the bottle tightly closed (HDPE bottles), or stored in the original package in order to protect from moisture and light (blisters) is acceptable. The shelf life after first opening of the bottle is 30 days at room temperature is subject to further justification and the applicant is recommended to address this in case of a future application.

2.4.3.5. 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.

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented.

During the procedure 7 MOs were raised by the CHMP related to 1) GMP documentation for the active substance manufacturers, 2) active substance starting materials justification from one manufacturer, 3) active substance starting materials justification from a second manufacturer, 4) incomplete discussion of impurities in active substance from the second manufacturer 5) impurity limit above the ICH Q3A qualification threshold 6) confirmatory testing of nitrosamines in active substance from the other manufacturer and 7) confirmatory testing in the finished product.

The MOs were satisfactorily resolved by: 1) submission of updated GMP documentation for manufacturing sites performing the critical micronisation step, 2-3) providing justifications for the selection of starting materials in accordance with ICHQ11, 4) performing a robust evaluation of all impurities likely to arise from the entire active substance synthesis 5) providing adequate evidence that the synthesis impurity is toxicologically qualified, 6-7) submitting confirmatory test results for six representative finished product batches manufactured using iloperidone from both active substance manufacturers, and in which nitrosamine was not detected.

Outstanding quality issues as other concerns remain, pertaining to submission of the complete version of the Applicant's Part of ASMF marked F120.EUDMF.O.E03 which should be enclosed in section 3.2.S presented by the Applicant, method validations of the analytical procedures for active substance from the other manufacturer, and an in-use stability for the finished product in the HDPE bottle.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the proposed product information. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendation(s) for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

Iloperidone Vanda Pharmaceuticals (iloperidone) has previously been the subject of two marketing authorization applications (MAAs). Both were full applications and neither resulted in a positive opinion. There were no unresolved non-clinical issues from the concluded procedures.

In the present application EMEA/H/C/006561/0000, no new non-clinical data was provided and the applicant submitted the same module 4 that was submitted in the last application. The maximum dose of iloperidone in the proposed indications remains the same.

A new ERA guideline has come into effect and the submitted ERA studies are therefore assessed in accordance with *Guideline on the environmental risk assessment of medicinal products for human use - Revision 1*, effective date: 01/09/2024.

2.5.2. 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.

2.5.2.1. 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 were initially 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. Although 5-HT2B agonists are known to be involved in the development of lung and heart fibrosis as well as valvular heart disease, there is no evidence to exclude the possibility that 5-HT2B antagonists may also have implications in human cardiac toxicity.

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 mention dependence potential of iloperidone in the RMP remains relevant (see safety discussion).

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 changed 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 with 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 etiology of schizophrenia.

2.5.2.2. 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.

2.5.2.3. 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%). hERG channel inhibition is predicted 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 is predicted to be clinically relevant.

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

The hERG IC50/Cmax values are as follows 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 u	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 10 nM 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.

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.

2.5.2.4. Pharmacodynamic drug interactions

See clinical pharmacology.

2.5.3. 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.

2.5.4. Toxicology

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

2.5.4.1. 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.

2.5.4.2. Repeat dose toxicity

Repeat-dose toxicology studies with iloperidone were conducted in mice, rats, rabbits and dogs up to 3 months in mice, 26 weeks in rats and 12 months in dogs following oral, intravenous or inhalation 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 has stated 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 should 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 was 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. Increased cholinesterase levels were 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. 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 $\geq$ 24-mg/kg). However, no dose limiting toxicities were observed and no NOAEL could be identified in the pivotal studies.

2.5.4.3. 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.

2.5.4.4. Carcinogenicity

Iloperidone was tested in a 2-year study in mice and in a 2-year study in rats.

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 was observed in females. 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). 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.

Iloperidone did not increase tumour incidence in a 2-year carcinogenicity study in Sprague Dawley rats at oral doses up to approximately 2.0 times the maximum recommended human dose (MRHD) of 24 mg/day on a mg/m2 basis.

2.5.4.5. Reproductive and developmental toxicity

The potential reproductive and developmental toxicity of orally administered iloperidone was evaluated in four studies. Iloperidone had no effect on male fertility, 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 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).

2.5.4.6. 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.

2.5.4.6.1. 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.

2.5.4.6.2. Studies with P95

P95 is the primary metabolite of iloperidone in humans with approximately 6 to 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 test 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.

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. Safety margins derived at NOAEL yields 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. 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 etiology 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. The iloperidone production intermediates P78 3784 and P90 9832 were not considered to be mutagenic in either the presence or absence of metabolic activation. Although P90 9834 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. Iloperidone intermediate Y8B, 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 (Y8A and 1-bromo-3-chloropropane) have been identified.

The proposed limits for the iloperidone related impurity Q7 (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 (refer to quality); this impurity was only present at a level of 0.44% (RC 5634).

A computational chemistry-based assessment of Q7 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 (compounds 014-99, 503-99B2 and 503-99B5) or moderate-confidence (504-99B7) 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 014-99, 503-99B2, 503-99B5 or 504-99B7 present a toxic threat at the very low concentrations manifest in the Iloperidone drug substance.

2.5.5. Ecotoxicity/environmental risk assessment

The submitted Environmental Risk Assessment (ERA) does not comply with the current guidelines. Consequently, no conclusions regarding environmental risks can be drawn at this stage.

The applicant has committed to submit an updated ERA post-marketing.

2.5.6. 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 5-HT2A compared to D2 receptors suggesting a reduced propensity for EPS development in comparison to typical antipsychotics like haloperidol. The in vitro data 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. Although 5-HT2B agonists are known to be involved in the development of lung and heart fibrosis as well as valvular heart disease, there is no evidence to exclude the possibility that 5-HT2B antagonists may also have implications in human cardiac toxicity. '*5-HT2B antagonistic effect'* as a missing information could not be found in the RMP. This concern was further addressed in the clinical section and is not further discussed in the non-clinical section.

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.

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.

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. In previous application it was agreed to not conduct additional studies but instead include "*Drug Abuse*" as Important missing information in the RMP. In the proposed RMP, this was not included and this concern was further addressed in the clinical section and is not further discussed in the nonclinical section.

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, additional non-clinical studies are deemed to not add further weight to the benefit/risk evaluation.

A toxicological programme was conducted with iloperidone including acute-toxicity, repeat-dose toxicity, reproductive and developmental toxicity, genotoxicity and carcinogenicity as well as other studies and studies on metabolites.

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 NOELs were established. Therefore, it is also questionable whether NOAELs can be established for the pivotal studies. Iloperidone administration induced 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. Increased cholinesterase levels were detected in male rats in a 4-week study but was not reproduced in the 13-week study. Margin of exposure animal/human was in general low, sometimes <1.

Iloperidone had no effect on male fertility, but had some effects on female reproduction, fetal and neonatal development. 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. 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 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 it difficult to perform any risk assessment. 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 not established.

Iloperidone is positive in the 3T3-NRU test and is distributed into melanin-containing tissues particularly in the eye.

A toxicological programme was also conducted on the major human metabolite P95. The clinical signs and tissue changes are widely compatible with those of the parent compound iloperidone.

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. Considering 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. 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.

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. Based on some findings in the reproductive and developmental studies and the lack of TK in these studies, a firm conclusion on the lack of teratogenic effect cannot be drawn. No significant mutagenic potential was determined in studies conducted with iloperidone or P95. A two-year carcinogenicity study with iloperidone in mice 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 was observed in females. The clinical relevance of these findings is unknown but iloperidone can be considered to have no carcinogenic potential. Iloperidone did not increase tumour incidence in a 2-year carcinogenicity study in Sprague Dawley rats at oral doses up to approximately 2.0 times the maximum recommended human dose (MRHD) of 24 mg/day on a mg/m2 basis. 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 very small for a non-life-threatening indication. However, it is not considered likely that further non-clinical studies or discussion will elaborate more 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.

Regarding the proposed product information, the pregnancy related parts should include relevant information and recommendations based on the non-clinical studies.

Regarding the ERA, the available data do not allow to conclude definitively on the potential risk of iloperidone to the environment.

The applicant committed to submit an updated ERA post-marketing.

2.5.7. Conclusion on the non-clinical aspects

In general, the applicant has submitted a comprehensive non-clinical package and there are no outstanding questions on PD, PK or toxicology. The product is considered acceptable from a non-clinical point of view.

However, an updated ERA should be provided post-authorisation.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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**

Table 1: Tabular overview of clinical studies

Study Number Sponsor (Country) Start/End Dates	Study Design	Treatment Regimen/Duration	Number of Subjects in Each Treatment Group	Sex (M/F) Age (yr): Median (range) Race: W/B/O	Primary Efficacy Endpoint
Phase 2 or 3, double-blind, placebo-controlled trials (schizophrenia)					
ILPB202 HMR (11 centers in USA) 02 Jul 93 – 31 Jan 95	6-week, multicenter, randomized, double-blind, parallel group, placebo-controlled	**Fixed titration/ maint. (Days 1-42)** BID regimen PBO, ILO 4 or 8 mg/d	Total=104 PBO=35 ILO 4 mg/d=35 ILO 8 mg/d=34	102M/2F 36 yr (18-54) Race: 66/31/7	Change from baseline in the PANSS total score of the iloperidone 4 mg/day and/or 8 mg/day groups versus placebo, LOCF analysis
ILP3000 Novartis (46 centers in USA) 24 Oct 98 – 17 Aug 99	6-week, multicenter, randomized, double-blind, parallel group, placebo and active-controlled, followed by 46 weeks active-controlled	**Fixed titration/ maint. (Days 1-42)** BID regimen PBO, ILO 4, 8, or 12 mg/d, or HAL 15 mg/d **Long-term flexible dosing (Days 43-364)** QD regimen ILO 4-16 mg/d or HAL 5-20 mg/d	**Study Days 1-42:** Total=621 PBO=127 ILO 4 mg/d=121 ILO 8 mg/d=125 ILO 12 mg/d=124 HAL 15 mg/d=124 **Study Days 43-364:** Total=232 ILO=192 HAL=40	442M/179F 39 yr (18-68) Race: 295/263/63	Change from baseline in the PANSS total score of iloperidone (mean of iloperidone 8 and 12 mg/day groups combined) as compared to placebo, LOCF analysis
ILP3004 Novartis (66 centers in the USA, Canada, Europe, and South Africa) 23 Jun 99 – 11 May 00	6-week, multicenter, randomized, double-blind,parallel group, placebo and active-controlled, followed by 46 weeks active-controlled	**Fixed titration/ maint. (Days 1-42)** BID regimen PBO, ILO 4-8 mg/d, ILO 10-16 mg/d, or RIS 4-8 mg/d **Long-term flexible dosing (Days 43-364)** QD regimen ILO 4-16 mg/d or RIS 2-8 mg/d	**Study Days 1-42:** Total=616 PBO=156 ILO 4-8 mg/d=153 ILO 10-16 mg/d=154 RIS 4-8 mg/d=153 **Study Days 43-364:** Total=294 ILO=219 HAL=75	433M/193F 39 yr (17-67) Race: 364/204/48	Change from baseline in BPRS score of iloperidone 10-16 mg/day group as compared to placebo, LOCF analysis
ILP3005 Novartis (67 centers in the USA,	6-week, multicenter, randomized, double-blind, parallel	**Fixed titration/flexible maint. (Days 1-42)** BID regimen PBO, ILO 12-16 mg/d, ILO	**Study Days 1-42:** Total=706 PBO=160 ILO 12-16 mg/d=244	435M/271F 39 yr (18-69) Race: 495/167/44	Change from baseline to endpoint in BPRS score of

Study Number Sponsor (Country) Start/End Dates	Study Design	Treatment Regimen/Duration	Number of Subjects in Each Treatment Group	Sex (M/F) Age (yr): Median (range) Race: W/B/O	Primary Efficacy Endpoint
Canada, Europe, and South Africa) 15 Apr 00 – 15 Mar 01	group, placebo and active-controlled, followed by 46 weeks active-controlled	20-24 mg/d, or RIS 6-8 mg/d	ILO 20-24 mg/d=145 RIS 6-8 mg/d=157 **Study Days 43-364:** Total=294 ILO=219 HAL=75		iloperidone 12-16 mg/day group as compared to placebo, LOCF analysis
VP-VVV-683-3101 Vanda Pharmaceuticals (44 centers total; 35 US, and 9 in India) 18 Nov 05 – 26 Sep 06	4-week, multicenter, randomized, double-blind, parallel group, placebo and active-controlled, followed by 25 weeks open label	**Fixed titration/flexible maint. (Days 1-28)** BID regimen PBO, ILO 24 mg/d, or ZIP 160 mg/d	**Study Days 1-28:** Total=593 PBO=149 ILO 24 mg/d=295 ZIP 160 mg/d=149	472M/121F 40 yr (18-65) Race: 208/299/86	Change from baseline to endpoint in PANSS-T score of iloperidone 24 mg/day group compared to placebo, MMRM analysis.
CILO522D2301 Novartis (66 centers total; 27 US, 15 India, 24 Ukraine)	Multicenter, double-blind, placebo-controlled, parallel-group, 26- week relapse prevention study followed by 52- week open label safety study	**Titration Phase (Week 1)** ILO: 1, 2, 4, 6, 6, 6, 6 BID **Open-Label Stabilization Phase (14-24 weeks)** ILO: 8-24 mg/day BID regimen, flexible dosing **Double-Blind Relapse Prevention Phase (26 weeks)** ILO: 8-24 mg/day BID regimen, flexible dosing PBO	**Interim Analysis Population** Titration/ Stabilization Phase: 587 Relapse Prevention Phase: ILO = 99 PBO = 96 **Final Analysis Population** Titration/ Stabilization Phase: 635	**Interim Analysis Population** Titration/ Stabilization Phase 369M/218F 39 yr (18-65) Race: 268/172/147 Relapse Prevention Phase 114M/81F 39 yr (18-64) Race: 133/44/18 **Final Analysis Population** Titration/ Stabilization Phase 400M/235F 40 yr (18-65) Race: 280/201/154 Relapse Prevention Phase 178M/125F	Time to relapse or impending relapse

Study Number Sponsor (Country) Start/End Dates	Study Design	Treatment Regimen/Duration	Number of Subjects in Each Treatment Group	Sex (M/F) Age (yr): Median (range) Race: W/B/O	Primary Efficacy Endpoint
				37 yr (18-64) Race: 151/59/93	
			Relapse Prevention Phase: ILO = 153 PBO = 150		Time to relapse or impending relapse
Phase 3, double-blind, active-controlled trials (schizophrenia)					
ILP3001 Novartis (51 centers Europe and Israel) 25 Jan 99 – 11 Jan 01	Multicenter, randomized, double-blind, active controlled, parallel group	**Fixed titration/flexible maint. (Days 1-42)** **Long-term flexible maint. (Days 43-364)** BID regimen ILO 4-16 mg/d or HAL 5-20 mg/d	Total=600 ILO=454 HAL=146	339M/261F 37 yr (18-69) Race: 591/1/8	Time to relapse
ILP3002 Novartis (35 centers in Asian Pacific Rim) 26 Jan 99 – 26 Jan 01	Multicenter, randomized, double-blind, active controlled, parallel group	**Fixed titration/flexible maint. (Days 1-42)** **Long-term flexible maint. (Days 43-364)** BID regimen ILO 4-16 mg/d or HAL 5-20 mg/d	Total=557 ILO=420 HAL=137	347M/210F 32 yrs (18-64) Race: 2/1/554	Time to relapse
ILP3003 Novartis (35 centers in South America) 16 Feb 99 – 18 Jan 01	Multicenter, randomized, double-blind, active controlled, parallel group	**Fixed titration/flexible maint. (Days 1-42)** **Long-term flexible maint. (Days 43-364)** BID regimen ILO 4-16 mg/d or HAL 5-20 mg/d	Total=487 ILO=365 HAL=122	310M/177F 35 yr (18-69) Race: 315/20/152	Time to relapse
Phase 3 double-blind placebo-controlled trials (bipolar mania)					
VP-VVV-683-3201 Vanda Pharmaceuticals 27 Centers (20 in the United States; 6 in Bulgaria; and 1 in Poland)	4-week, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of iloperidone for 4 weeks in the	**Fixed titration and maint. (Days 1-28)** BID regimen PBO or ILO 24 mg/d* *note CYP2D6 PM's received 12mg/d. All groups received	Study Days 1-28: Total=414 PBO=206 ILO 24 mg/d=208	N=414 228M/186F 46yr (18 to 65) Race: 265/117/32	Change from baseline to endpoint in YMRS total score of iloperidone 24 mg/day group compared to placebo, MMRM analysis.

Study Number Sponsor (Country) Start/End Dates	Study Design	Treatment Regimen/Duration	Number of Subjects in Each Treatment Group	Sex (M/F) Age (yr): Median (range) Race: W/B/O	Primary Efficacy Endpoint
04 Apr 2021 – 07 Sept 2022	treatment of patients with acute manic episodes associated with bipolar I disorder	bid.			

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

The formulation applied for is immediate release tablets and contains 1, 2, 4, 6, 8, 10 and 12 mg of iloperidone. The proposed starting dose is 1 mg orally BID, that should be slowly titrated to reach a target range of 6-12 mg BID (maximum dose 12 mg BID).

The study package contains biopharmaceutic studies (BE and food effect), two mass balance studies, studies in renal as well as hepatic impairment, a study investigating the effect of CYP26 polymorphism and some DDI studies. An in vitro package characterising in vitro metabolism, transporters, protein binding, as well as potential to inhibit or induce enzymes or transporters is also provided.

Iloperidone has two major metabolites, P88 (with similar activity as iloperidone) and P95 (regarded by the Applicant as inactive).

Methods

A validated method for determination of iloperidone and metabolites P88 and P95 in plasma using LC/MS/MS was used in most studies (DMPK(US) R99-2297). Additional method validations for determination of analytes in plasma were referred to in certain studies (e.g. MPLM 02.418.01). There was also a method for determination of iloperidone and metabolites in urine (DMPK(US) R98-3042).

The pharmacokinetic parameters of iloperidone were determined by non-compartmental methods. For statistical analysis, descriptive statistics and ANOVA were used. Pharmacokinetics were also analysed by means of non-linear mixed effects modelling.

Absorption

The peak plasma concentrations of iloperidone are observed approximately 2-4 hours after administration, and for P88 and P95, after approximately 4 and 6 hours based on single-dose data in healthy volunteers. In a multiple dose study in patients, tmax was 1.5-2 hours for iloperidone and 2.5-3 hours for P88 and P95 (study ILO5220112).

Study ILO5220105 investigated the effect of food on the final marketing formulation (FMF-T) at a dose of 3 mg. A high fat meal slightly reduced the rate of absorption for iloperidone and the active metabolites P88 and P95 but did not affect the extent of absorption (results for AUC_{0-t} and $AUC_{0-\infty}$ for iloperidone (and metabolites) were within conventional bioequivalence criteria). Tmax was delayed by 1 hour for iloperidone, 2 hours for P88 and 6 hours for P95.

In vitro results do not indicate that iloperidone or its major metabolites are substrates for P-gp or BCRP.

The absolute bioavailability is unknown because no intravenous formulation has been administered.

The relative bioavailability of a 3-mg dose of the tablet (final marketing formulation) was approximately 96% as compared with a 3 mg oral solution under fasted conditions (study ILO5220105).

Studies were performed to determine if different formulations used during the clinical development were bioequivalent to each other. Study ILPB106 compared a tablet formulation (CSF) to an early capsule formulation in the fed state and iloperidone results were within criteria for bioequivalence. Study ILO5220110 demonstrated bioequivalence in the fasted state for Cmax and AUC0-t of iloperidone between final market formulation (FMF-T) and two over-encapsulated formulations used in

pivotal phase III studies (CSF-C and FMF-C). Study VP-VYV-683-1002 compared the final marketing formulation (FMF-T) to the over-encapsulated iloperidone tablet (used in the phase III study VP-VYV-683-3101 for blinding purposes) under fed conditions. Bioequivalence was demonstrated for AUC_{0-t} but the C_{max} confidence interval fell slightly outside 80.00-125.00% (upper limit 127%).

Distribution

Iloperidone has an apparent volume of distribution of 1340-2800L.

Based on the in vitro study XS-0531 using ultracentrifugation, iloperidone was highly protein bound (>99.0%) and its metabolites had slightly lower protein binding (98% for P88 and 94% for P95).

The average blood to plasma ratio in humans was approximately 0.6.

Elimination

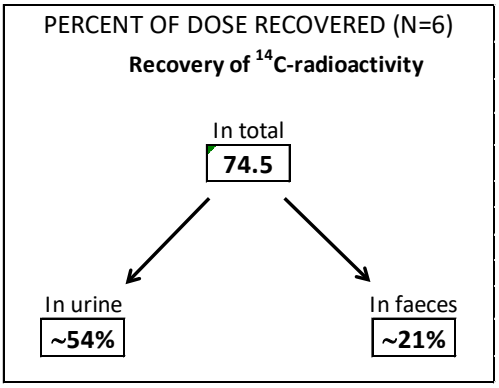
Iloperidone is almost exclusively eliminated by hepatic metabolism with a clearance (CL/F) of *ca* 116 L/h and a terminal half-life around 18 hours (in CYP2D6 EMs). There are two major circulating metabolites in plasma; P95 which formation is mediated by CYP2D6, and P88 which results from reduction. The half-lives of these metabolites are slightly longer than that of parent drug (23-26 h).

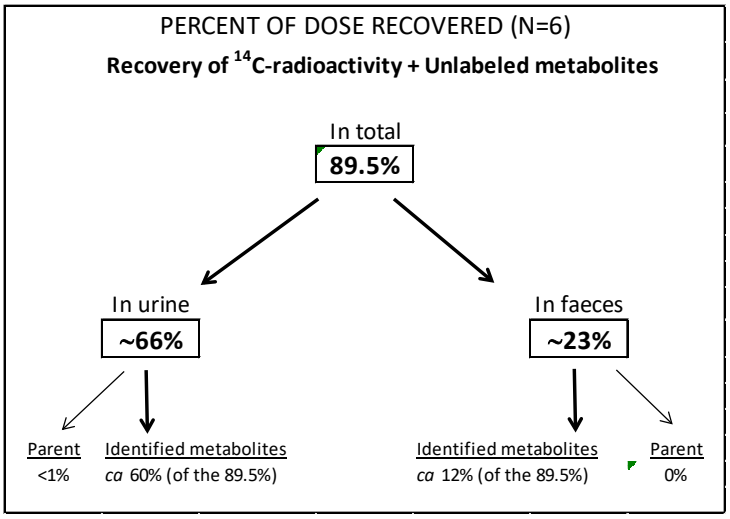
In poor metabolisers, CL/F was 66 L/h and the half-lives of parent drug and metabolites were longer (33, 37, and 31 hours for iloperidone, P88 and P95, respectively) (study ILO5220104).

Two mass-balance studies with [^{14}C]-labelled iloperidone were performed in healthy male subjects, one study in three subjects with unidentified CYP2D6 genotype and one in six subjects including 4 EM and 2 PM (study ILO522 A2301, presented below). The 3 mg/kg single dose was administered as an oral solution. The results of study ILO522 A2301 showed that iloperidone is solely eliminated by metabolism since <1% of the parent compound was excreted unchanged in urine and none in faces. The plasma clearance (CL/F) of iloperidone (estimated based on mean plasma concentration data) was *ca* 100 L/h in extensive metabolizers and approximately 50% lower in poor metabolizers. The estimated terminal plasma half-life of iloperidone in EM subjects was 19h, and somewhat longer for the major circulating metabolites (23-28h). Only for P88, there appeared to be a difference in $t_{1/2z}$ in the PM subjects (13h versus 23h in EM).

The recovery of radioactivity within 14 days after dosing was in the order of 74%, the main part excreted in urine, i.e. *ca* 52-56%, and about 20% recovered in faeces. When estimating the recovery as the sum of radioactivity and identified unlabelled metabolites, the mean total recovery was 89.5±8.1%. The total recovery was not statistically different between EM (range 78.5-93.6%) and PM (range 81.1-91.2%) of CYP2D6.

There were at least 10 radio-labelled metabolites, and at least 2 unlabelled metabolites characterized and quantitated in the excreta. The main metabolites included P95 (13.8%) and its glucuronide (P26.1, 10.8%); *S*-P88 (5.8%) and its glucuronide (P27.4, 1.5%); *N*-dealkylation product (P20.8, 6.5%) and its carbonyl-reduced product (P17.6, 8.9%); P28.2 (4.8%), and unlabelled metabolites (P36.3 and its conjugate, 9.8%; open ring P36.3 and its conjugate, 5.1%). The total amount of metabolites characterized accounted for 71.5% of the dose, or 80% of the recovered dose.





Based on in vitro-data, iloperidone was metabolized in human liver microsomes to primarily form 4 products: P22 (N-dealkylation), P94 (hydroxylation), P89 (*O*-demethylation), and P88 (carbonyl reduction). Iloperidone was metabolized by CYP2D6 to form primarily P94 and the minor products, P22 and P31.2, and was metabolized by CYP3A4 to form primarily the products P89 and P22.

The major drug-related circulating components in the mass-balance study included iloperidone, P95, P88, P20.8, and P24.6, which were together accounted for 88-91% of the total plasma exposure.

P95 and P88 are considered major based on their plasma exposure. Following a 3 mg/kg oral single dose of [^{14}C]-iloperidone in healthy male subjects, four extensive metabolizers and two poor metabolizers of CYP2D6, P95 accounted for 47.9% and 22.7% of total plasma exposure in EM and PM, respectively, and P88 for 19.5% (EM) and 34.0% (PM). The exposure of P95 approximately equals the sum of exposures for iloperidone and P88.

Iloperidone is metabolized via several pathways:

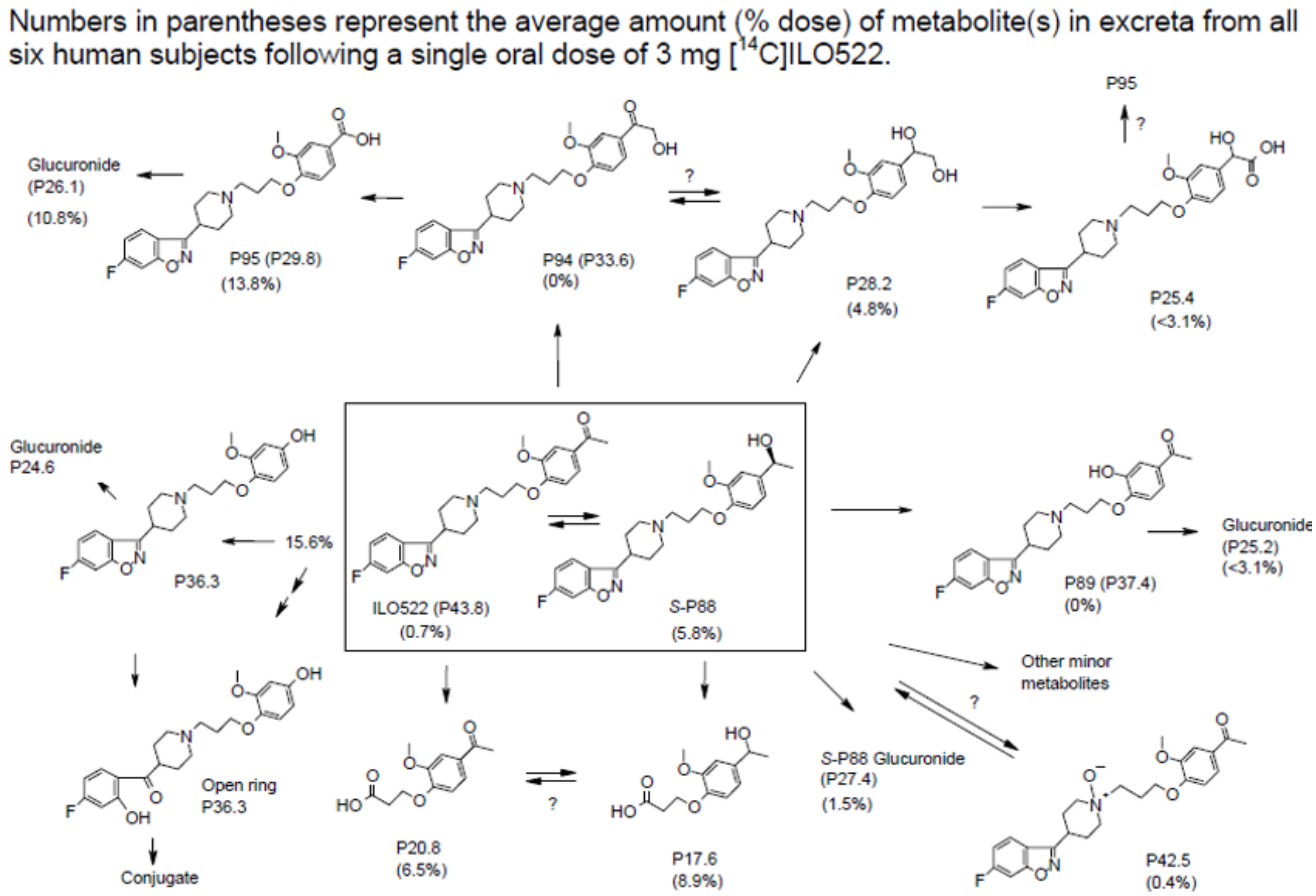
Hydroxylation to P94, an α-hydroxy ketone metabolite, mediated by CYP2D6. This metabolite then undergoes further oxidation and decarboxylation via CYP2D6 to form P95. P94 is not detected in plasma, likely because the reaction is very rapid. Approximately 25 % of the dose is eliminated via this pathway.

O-demethylation to P89 involving CYP3A4, as well as formation of other cleavage products and phenol-type compounds. This metabolic pathway appears to be of less importance since such a low fraction of the dose forms P89 and its further glucuronide.

Carbonyl reduction to form P88 via carbonyl reductase. Approximately 20 % is excreted this way. The main metabolites formed from S-P88 are P17.6 and a glucuronide of S-P88.

Additional oxidative and reductive steps lead to further biotransformation products. Excreted metabolites are highly conjugated as glucuronides and sulphates.

Figure 2: Biotransformation scheme of iloperidone (ILO522) in man



The parent compound and P95 are achiral while metabolite P88 has a chiral centre and exists in an R- and an S-form. Only the S-isomer of P88 was found in human plasma and urine.

Two metabolites were considered major based on their plasma exposure i.e. P95, which is formed from iloperidone in two oxidative steps mediated by CYP2D6, and P88, which is a reduced form of the parent compound. Plasma concentrations of P95 and P88 were determined in several studies, both in healthy subjects and patients (see section Dose proportionality below). The metabolite to parent compound exposure ratios ranged from 2.0 to 1.6 for P88/Iloperidone and from 4.2 to 3.2 for P95/Iloperidone. For both metabolites, the ratios decreased with increasing dose of iloperidone.

CYP2D6 is polymorphic with approximately 7-10% of the Caucasian population categorized as poor metabolizers of this isozyme. Genetic polymorphism of CYP2D6 have a significant impact on the pharmacokinetics of iloperidone in humans, which was investigated in study ILO522 0104, comparing pharmacokinetics of iloperidone in subjects genotyped as extensive or poor metabolizers of CYP2D6. In the performed study, the clearance (CL/F) of iloperidone was reduced by 43% in poor compared to extensive metabolizers which resulted in a 1.6-fold increase in AUC of the parent compound. The exposure of P95 was as expected much lower in PM than in EM subjects with an observed reduction in both AUC and C_{max} of *ca* 80%. The exposure of metabolite P88 was also significantly affected by the CYP2D6 genotype status. The AUC was 2-fold higher, and the mean $t_{1/2z}$ was 50% longer, in PM subjects compared EM subjects.

Table 2: 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 3: 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)

Table 4: Mean (CV%) P95 pharmacokinetic parameters in extensive and poor CYP2D6 metabolizers following a 3 mg single oral dose of iloperidone

P95 PK Parameters	Mean (CV%)		
	Extensive (N=18)	Poor (N=8)	% Difference [a]
t_{max} (h) [b]	6.0 (3-16)	8.0 (3-12)	--
C_{max} (ng/mL)	4.5 (34)	0.67 (44)	-85.0
$AUC_{0-\infty}$ (ng*hr/mL)	153.8 (26)	32.1 (36)	-79.1
$t_{½}$ (h)	23.0 (20)	30.6 (31)	33.0
CL_T/F (L/hr)	21.5 (41)	101.4 (26)	380.9
V_Z/F (L)	730.3 (53)	4,520 (53)	519.1
Ae (% of dose)	19.2 (31)	4.5 (24)	-76.5

P95 PK Parameters	Mean (CV%)		
	Extensive (N=18)	Poor (N=8)	% Difference [a]
CL_R (mL/min)	66.4 (26)	75.0 (25)	12.9

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

Dose proportionality and time dependencies

The dose proportionality of iloperidone at steady state in 28 schizophrenic patients (32 enrolled (2 female, 30 male), 2 identified as CYP2D6 PMs, 28 provided PK data), following multiple doses of 2, 4, 8 and 12 mg b.i.d was investigated (study ILO5220112).

Following administration of 2, 4, 8, and 12 mg b.i.d. doses of iloperidone, the iloperidone AUC_T increased 2.2-, 4.4-, and 7.7-fold with 2-, 4-, 6-fold increases in dose. The iloperidone C_{maxss} increased similarly with dose. Thus, it appears that from 2 mg to 8 mg b.i.d. doses, iloperidone showed dose proportionality, but showed slight deviation from dose proportionality following 12 mg b.i.d. dosing.

Table 5: Mean (CV%) iloperidone pharmacokinetic parameters in schizophrenic patients following multiple oral doses 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

The AUC_T and Cmaxss for P88 showed a 2.1-, 4.2-, and 6.4-fold increase with 2, 4, 8, and 12 mg b.i.d. doses.

Table 6: Mean (CV%) P88 pharmacokinetic parameters in schizophrenic patients following multiple oral doses of iloperidone

Parameters	Mean (CV%)			
	2.0 mg	4.0 mg	8.0 mg	12.0 mg
t_{max}^{ss} (h)*	2.5 (39)	2.5 (44)	2.5 (50)	3.0 (28)
C_{max}^{ss} (ng/mL)	5.82 (39)	12.00 (45)	24.63 (47)	37.09 (34)
C_{min}^{ss} (ng/mL)	3.25 (44)	6.74 (59)	12.89 (50)	20.41 (43)
AUC_t (ng•h/ml)	52.56 (39)	108.5(48)	220.2 (44)	335.5 (36)
C_{avg}^{ss} (ng/mL)	4.38 (39)	9.04 (48)	18.35(44)	27.96 (36)
N	28	24	20	16

*Median (Range)

The AUCT and Cmaxss for P95 showed 2.1-, 4.3-, and 6.4-fold increases following 2, 4, 8, and 12 mg b.i.d. doses of iloperidone.

Table 7: Mean (CV%) P95 pharmacokinetic parameters in schizophrenic patients following multiple oral does of iloperidone

Parameters	Mean (CV%)			
	2.0 mg	4.0 mg	8.0 mg	12.0 mg
t_{max}^{ss} (h)*	2.8 (67)	2.5 (69)	2.5 (70)	2.8 (33)
C_{max}^{ss} (ng/mL)	9.02 (41)	19.06 (39)	37.74 (37)	58.48 (38)
C_{min}^{ss} (ng/mL)	5.80 (43)	12.00 (32)	24.72 (29)	36.65 (32)
AUC_t (ng•h/ml)	88.99 (37)	187.1 (34)	379.7 (32)	568.9 (35)
C_{avg}^{ss} (ng/mL)	7.42 (37)	15.59 (34)	31.64 (32)	47.41 (35)
N	28	24	20	16

*Median (Range)

No specific discussion about time dependency has been presented by the Applicant. In study ILO522 0112 the mean (CV%) iloperidone Cmaxss values were 4.12 (58%), 8.87 (53%), 18.93 (45%) and 32.14 (43%) ng/mL, respectively for the 2.0, 4.0, 8.0, and 12.0 mg b.i.d. doses. Considering that Cmax of iloperidone after a single dose of 3 mg was on the order of 3 ng/mL, and assuming dose-proportionality, accumulation of iloperidone with multiple dosing appears to be at least two-fold.

Intra- and inter-individual variability

Inter-and intra-individual variability in healthy volunteers is available from study ILPB 106 (replicate design BE study in healthy volunteers in the fed state at a dose of 3 mg, n=30). Intra-individual variability was about 15-20 CV% in healthy volunteers and inter-individual variability was about 30-40%. There was a high between-subject variability for AUC and Cmax for iloperidone in the dose-proportionality study in schizophrenic patients (study ILO5220112), between 45 and 65%.

Pharmacokinetics in the target population and therapeutic window

All clinical pharmacology studies in healthy volunteers were performed with a single dose of 3 mg or less. Considering dose-proportionality, and with an expected accumulation of 2-fold, these single dose

values in healthy volunteers can be compared to multiple-dose data from the dose-proportionality study in schizophrenic patients (study ILO5220112). Overall, these comparisons indicate that there are no major differences in PK between healthy volunteers and patients with schizophrenia.

No discussion has been provided by the Applicant regarding the therapeutic window of iloperidone. Dose adjustments (reduction of the (maximal) dose by half) are proposed in CYP2D6 poor metabolisers and patients taking strong CYP2D6 or CYP3A4 inhibitors.

Special populations

A dedicated renal impairment study (ILO-0522A-0102) investigated the effect of severe renal impairment (here defined as subjects with CrCL <30 ml/min based on the Cockroft-Gault formula and on hemodialysis) on the PK of iloperidone (given as a single 3 mg dose) and metabolites. No study in patients with mild or moderate renal impairment was performed. In patients with severe renal impairment, the exposure of iloperidone was increased approximately 1.5-fold, P88 was decreased to approximately 0.7-fold and P95 significantly increased up to 3-fold, if based on $AUC_{0-\infty}$ and the point estimates in the ANOVA. By comparing mean $AUC_{0-\infty}$ values, iloperidone exposure was increased by 80% in patients with severe RI.

Two dedicated hepatic impairment studies were performed, comparing the PK of iloperidone and metabolites in subjects with mild or moderate hepatic impairment to healthy controls. No study in severe hepatic impairment has been performed. The main study is ILO522 D2401, performed at a single dose of 2 mg iloperidone. In this study, exposure of iloperidone in total plasma was similar between different groups. The unbound fraction of iloperidone, P88 and P95 was however higher in subjects with moderate hepatic impairment than in healthy subjects and subjects with mild hepatic impairment. Subjects with moderate hepatic impairment had a higher (about 2-fold) and more variable exposure to free P88, but similar exposures to free Iloperidone and free P95, compared to normal subjects and subjects with mild hepatic impairment (mild HI and normal subjects had similar free exposures of both iloperidone and metabolites).

Body weight does not appear to have a clinically relevant impact on exposure (Cmax,ss) of iloperidone. Gender does not appear to have a clinically relevant impact on exposure (Cmax,ss) for each of iloperidone, P88, and P95 (Study VP-VVV-683-3201).

No specific study was conducted to evaluate the effect of race or ethnic origin. In population PK analysis, no correlation was found between race (Caucasian, African-American, Asian, other) and plasma exposure (VP-VYY-683-3101-PK01).

No specific study was conducted to evaluate the effect of age.

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
PK Trials	0/674[a]	0/674	0/674

[a] One Subject (#18) who was 66 years old when dosed with iloperidone in Study ilo0102 was not included in the pharmacokinetic and statistical analyses.

Total number= all subjects included in the bioavailability and pharmacokinetic studies

No specific study was conducted to evaluate PK in children or adolescents, and these populations were not used in clinical trials.

Pharmacokinetic interaction studies

Effect of other Co-administered drugs on iloperidone pharmacokinetics (Victim)

Study ILO5220107 investigated the effect of multiple doses of the strong CYP3A4 inhibitor ketoconazole on the exposure of iloperidone and metabolites following a single 3 mg iloperidone dose in CYP2D6 extensive metabolisers. AUC and Cmax of iloperidone and P88 increased about 1.6-fold in CYP2D6 extensive metabolisers. The increase in exposure for P95 was somewhat lower (1.4-fold).

Study ILO5220108 investigated the effect of multiple doses of the strong CYP2D6 inhibitor fluoxetine on the exposure of iloperidone and metabolites following a single 3 mg iloperidone dose in CYP2D6 extensive metabolisers. Iloperidone exposure increased 2.4 - fold and for P88, the increase was of the same order, i.e. 2.2 - fold. For P95, the exposure decreased upon co-administration and was approximately 0.4-fold.

In the thorough QT study ILO522-2328 effects of co-administration of both paroxetine (strong CYP2D6 inhibitor) and ketoconazole was investigated in patients with schizophrenia or schizoaffective disorder. Steady state C_{max} of iloperidone and P88 increased 1.6-1.7-fold with concomitant administration of the strong CYP2D6 inhibitor paroxetine and with combined administration of paroxetine and the strong CYP3A4 inhibitor ketoconazole the increase was even higher, 2.3-fold for iloperidone and 2.3-2.7-fold for P88. Effects on AUC were not determined.

Effect of Iloperidone on the pharmacokinetics of co-administered drugs (Perpetrator)

Study ILO5220104 investigated the interaction between iloperidone and the CYP2D6 probe substrate dextromethorphan in CYP2D6 extensive metabolisers. There were no large effects of iloperidone on dextromethorphan exposure, thus not indicating relevant CYP2D6 inhibition by iloperidone.

Study CILO522E2101 investigated the effects of multiple doses of iloperidone (6, 8 and 10 mg BID) on the exposure of the CYP3A4 probe substrate midazolam. The study results indicate that iloperidone is a mild CYP3A4 inhibitor, with up to 1.5-fold increases in AUC of midazolam.

Pharmacokinetics using human biomaterials

Table 8: Cut-offs for the evaluation of interaction potential (based on EMA DDI guideline)

	50×Cmax(u)[a] (µM)	25×Inlet Cmax(u)[a] (µM)	0.1×dose/250 ml[b] (µM)
Parent drug iloperidone	0.04	0.75	11.3
Metabolite P88	0.086	NA	NA
Metabolite P95	0.41	NA	NA

a Multiple dose Cmax, 12 mg BID dose (study ILO522012-dose proportionality in schizophrenic patients): 32 ng/ml (0.075 µM) for iloperidone, 37 ng/ml (0.086 µM) for P88 and 59 ng/ml (0.137 uM) for P95. Fu 1% (iloperidone), 2% (P88) and 6% (P95).
b Based on a 12 mg dose
NA - Not applicable

Based on ICH M12, the following cut-offs for transporter inhibition are calculated for iloperidone:

10×Inlet Cmax(u) (for OATP1B1 and 1B3, instead of 25xinlet Cmax (u)): 0.3 µM

10×Cmax(u) (for OAT1, OAT3, OCT2): 0.008 µM

There is an in vitro signal of CYP3A4 inhibition by iloperidone (direct inhibition in the intestine as well as TDI) and also an in vitro signal of CYP43A4 inhibition (TDI) for metabolite P88. There are no in vitro signals of in vivo relevant inhibition of any other CYP enzyme.

There is a signal of in vitro induction of CYP3A4 but not of CYP2B6. Induction data regarding CYP1A2 are inconclusive.

There is a signal of in vivo relevant inhibition of intestinal P-gp by iloperidone. There is no signal of clinically relevant inhibition of any other transporter by iloperidone or metabolites based on in vitro data.

In vitro results do not indicate that iloperidone or its major metabolites are substrates for P-gp or BCRP. It cannot currently be concluded if iloperidone is a substrate of hepatic uptake transporters OATP1B1 or OATP1B3, or if renal or hepatic transporters are involved in the disposition of P88 or P95, except that in vitro-data indicate that metabolite P95 is a substrate of the renal uptake transporter OAT3.

Exposure relevant for safety evaluation

The mean (%CV) exposure of iloperidone, P88 and P95 after multiple doses of 12 mg b.i.d. to schizophrenic patients is 232 (48), 336 (36) and 570 (35) ng*h/ml (AUC_{τ} 0-12 hours). The corresponding mean (%CV) maximal concentrations of iloperidone, P88 and P95 at steady state are 32 (43), 37 (34) and 59 (38) ng/ml (data based on study ILO522012-dose proportionality in schizophrenic patients).

In CYP2D6 poor metabolizers AUC of iloperidone increases by 1.6 fold, AUC of P88 increases by 2 fold, and Cmax of P88 increases by 1.4 fold (and exposure for P95 decreases).

Subjects with moderate hepatic impairment had a nearly 2-fold increase in P88 AUC.

Severe renal impairment appeared to be associated with an up to 80% increase in Iloperidone exposure and a 3-fold increase in P95 exposure.

The popPK model has indicated that there may be higher exposure in women than in men.

2.6.2.2. Pharmacodynamics

Mechanism of action

Iloperidone is a piperidinyl benzisoxazole derivative developed for treatment of the symptoms of schizophrenia. *In vitro* receptor profiling using radioligands, non-clinical pharmacology studies, and second messenger assays have demonstrated that iloperidone has high (nM) affinity for $5HT_{2A}/NE_{a1}/NE_{a2C}/D_2/D_3/5\text{-}HT_{1A}$ receptors in humans and acts as an antagonist at selected dopaminergic, serotoninergic, and adrenergic receptors. The Applicant claimed that the binding profile would predict that iloperidone is likely to have antipsychotic effects similar to atypical antipsychotics, with reduced liability for extrapyramidal signs and symptoms.

Primary and Secondary pharmacology

The Applicant has not presented any primary pharmacology studies in man, such as PET imaging studies. The pharmacology of iloperidone was investigated through non-clinical and several clinical studies. In vitro studies indicate that the affinity of iloperidone was found to be highest for human $5\text{-}HT_{1A}$, $5HT_{2A}$, D_2, D_3, adrenergic alpha1 and alpha2 receptors, and lower for D1, D5, and other serotonergic receptors.

The predominant circulating active metabolites of iloperidone in humans are P95 and P88. P88 crosses the blood-brain barrier, while P95 does not do so detectably.

Iloperidone and its metabolites P88 and P95 are potent alpha 1 antagonists, with Ki values of 0.36nM, 8.31nM4, and 4.7nM, respectively. The peripheral actions of alpha 1 receptor antagonists relax smooth muscle cells of blood vessels, which results in decreased vascular resistance which can have a variety of effects including decreased systolic and diastolic blood pressures.

QTc prolongation is of primary concern with regard to the secondary pharmacology of iloperidone and its metabolite P88. The applicant has conducted a TQT-study and a concentration-QTc analysis of part of the results. Both iloperidone and its active metabolite P88 contribute to QT prolongation, with a statistically significant association between their concentrations and QT changes ($p < 0.01$ for iloperidone; $p < 0.02$ for P88) (please refer to 2.6.8 Clinical Safety).

The P95 metabolite (based on its calculated safety margin from hERG data *in vitro*) is predicted to carry a low risk for QTc-prolongation *in vivo* in humans, at clinically relevant concentrations. The relative contribution of P95 to other clinical effects is unclear.

2.6.3. Discussion on clinical pharmacology

Iloperidone is a new chemical entity; and the pharmacokinetic studies should thus aim at describing the disposition and to identify subgroups where an altered exposure can be expected based on the pharmacokinetic properties. Potential interactions should also be evaluated.

All the pharmacokinetic studies now submitted were included in the previous application in 2015; from a pharmacokinetic perspective, grounds for refusal were related to risk of QT prolongation in relation to DDIs and genetic polymorphism.

Of the two major metabolites of iloperidone, P88 can be considered an active metabolite with similar actions as the parent compound. Regarding P95, the contributions to clinical effects are unclear; it is considered questionable to regard P95 as inactive and it may also contribute to adverse events but is predicted to not cause QT prolongation at clinically relevant concentrations. The main occasion where P95 is increased is in case of renal impairment, and this needs to be considered as discussed below.

Iloperidone is proposed for the treatment of patients with schizophrenia and with bipolar disorder. The standard target dose is proposed to be in the range of 6-12 mg BID (12 to 24 mg/day), with potential dose reduction during concomitant treatment with strong CYP3A4 or CYP2D6 inhibitors as well as in patients being poor metabolizers of CYP2D6.

Methods

The pharmacokinetic and statistical methods which were used, are standard.

Bioanalytical methods

The bioanalytical method validation was performed long before the EU bioanalytical guideline came into force in 2012 and there are deviations from guideline requirements, e.g. no assessment of matrix effect was performed. However, the main method used for analysis in plasma in most studies, R99-2297, is generally considered sufficiently validated. Also, the methods used in studies VP-VYV-683-100 and ILO522 D2401 are considered sufficiently validated.

Population PK model

The applicant used data from phase I studies VP-VYV-683-1001 and CILO5220105 to develop a population PK model. Subsequently, the pharmacokinetic model was then applied to the phase 3 data by fixing the values for the structural model (thetas) and estimating the IIV for all other parameters, and covariate effects were evaluated. Major issues with the data and the model development approach have been identified. The population PK analysis is not considered acceptable for use in accordance

with its intended purpose. The phase 3 data are not sampled in a manner that provides data with sufficient information for the covariate analysis. Despite an unreliable analysis, it is a concern that women were found to have a 50% higher bioavailability (50% higher exposure) compared to men. As a clinically relevant and significant side effect from Iloperidone treatment is QT-prolongation, it needs to be fully investigated whether this is a true difference between men and women or an artifact of limited data and inadequate model development. As the model is not reliable the resulting questions may be answered through other analyses than population PK modelling. Therefore, the issues with the population PK model are not pursued further. The model needs major updates if it is going to be used for predictions/simulations. The relationship between concentration and CYP2D6 polymorphism is assessed in separate sections.

Absorption

Solubility data has not been presented in the entire pH range of 1.2–6.8 at 37±1°C relevant for BCS classification, but the Applicant concludes that iloperidone is not highly soluble. The Applicant has presented predictions and good arguments based on data from the mass balance studies that the absorption is complete in humans. Although no firm conclusion can be drawn in the absence of intravenous data it is agreed that the fraction of dose absorbed in man is likely to be ≥85%. Thus, iloperidone can be considered a highly permeable substance according to the BCS biowaiver criteria. Iloperidone is thus regarded as a BCS class II substance.

The absolute bioavailability is not known. Although the fraction of dose absorbed is high, the absolute bioavailability is considerably lower due to first pass metabolism. First-pass effect is smaller in slow metabolizers due to lower CYP2D6 activity.

Administration of iloperidone with a high fat meal slightly reduced the rate of absorption for iloperidone and the metabolites P88 and P95 but did not affect the extent of absorption. It is agreed that the product can be taken with or without food.

Overall, bioequivalence has been demonstrated between the different formulations used during the clinical development and in particular between the final formulation for marketing and the formulations used in the phase 3 studies (except for a minor deviation from bioequivalence regarding C_{max} in study VP-VYV-683-1002 which is not considered clinically relevant). Two of the studies were performed in the fed state (standardised breakfast). Since the product is intended to be taken regardless of food, a BE study should generally be performed in the fasted state as this is considered the most sensitive situation to detect differences between formulations. However, as there is no relevant food effect, the performance of the studies in the fed state should not invalidate the studies. Also, study ILO5220110 is considered the most important BE study, and this study was performed in the fasted state.

Distribution

Iloperidone exhibits a very large volume of distribution, averaging between 1340 and 2800 L, with observed extremes ranging from 1179.2 to 6312.6 L. This high volume of distribution indicates extensive penetration into organs and tissues. Iloperidone is highly bound to plasma proteins (>99%) and its metabolites had slightly lower protein binding (98% for P88 and 94% for P95).

Elimination and metabolism

Iloperidone is almost exclusively eliminated by hepatic metabolism, as unchanged parent compound in the excreta accounts for less than 1% of total radioactivity administered in the radiolabel ADME study. The terminal half-life is around 18 hours (in CYP2D6 EMs). There are two major circulating metabolites in plasma; P95 which formation is mediated by CYP2D6, and P88 which results from reduction.

The mean total recovery and the total amount of metabolites characterized of the mass-balance study ILO522 A2301 is found acceptable. The dose was mainly excreted in urine (ca 66%) and partly biliary excreted into faeces (ca 23%). The observed long terminal half-life of total plasma radioactivity and the slow recovery in the excreta was not associated with any of the identified metabolites. According to the Applicant, it may be explained by the formation of metabolites that subsequently (acetic acid and/or acetaldehyde moieties) were incorporated into the carbon pool for biosynthesis. This hypothesis is found acceptable.

The two major metabolites have almost identical molecular mass as the parent compound which enables a direct comparison of their relative plasma concentration expressed in ng/ml. The metabolites are somewhat less bound to plasma proteins though, so the free concentrations are expected to be higher for P95 ($f_{unbound}$ 5%) and P88 (f_u 3%) than for iloperidone (f_u ≤1%).

It is agreed with applicant that P88 should be considered an active metabolite since its receptor binding profile *in vitro* is very similar to iloperidone. It is also agreed with the applicant that P95 (based on its calculated safety margin from hERG data *in vitro*) has a predicted low risk for QTc-prolongation *in vivo* in man at clinically relevant concentrations.

The relative contribution of P95 to other clinical effects is difficult to evaluate though. According to the applicant, P95 has the potential to exert clinically relevant effects due to interaction with peripheral receptor subtypes but cannot cross the blood-brain barrier and is not expected to exert pharmacological effects on the central nervous system. However, the latter is contradicted by preclinical data in the rat, where the observed CNS-effects of P95 were similar to those of iloperidone. Furthermore, the exact mechanism of action of iloperidone in schizophrenia and bipolar I disorder has not been fully elucidated and hence it is not known to what extent the observed primary pharmacological effect is CNS-mediated. It would have been preferrable if the applicant had collected CSF data in order to estimate the concentrations at the presumed site of action within CNS, but this issue is not pursued.

The plasma exposure of the major metabolites P88 and P95 is considered to have been adequately evaluated in healthy subjects and in patients with schizophrenia.

As compared to extensive metabolizers of CYP2D6, poor metabolizers have 1.6-fold higher AUC exposure of iloperidone, a 2-fold higher exposure of P88, but an 80% lower exposure of P95 based on the results of study ILO522 0104. This study confirms the role of CYP2D6 in iloperidone metabolism and clearance and that the formation of P95 is predominantly mediated by CYP2D6 *in vivo* in humans. The effects on P88 suggests a shift in metabolism of iloperidone to the P88 pathway in PM subjects and also indicates that P88 may be further metabolized by CYP2D6.

CYP2D6 is known to be highly polymorphically expressed, and several genetic variants of functional relevance are known, that occur in a considerably high frequency in the European population. Today, PM, IMs, EMs and UMs of CYP2D6 are well defined based on those specific allelic combinations/genotypes as summarized in the well-established data sources PharmVar/PharmGKB. In study ILO522 0104, not all currently known "no function" and "decreased function" alleles were investigated. There may therefore be a risk that the effect of CYP2D6 polymorphisms on iloperidone and P88 exposure (1.6-fold increase of iloperidone) has been underestimated, supported by the fact that the effect of a strong CYP2D6 inhibitor on iloperidone exposure was larger (2.4-fold). A similar increase in iloperidone exposure between EMs and PMs as that caused by a strong CYP2D6 inhibitor would be expected. A more extensive and differentiated genotyping was performed in phase 3 study VP-VYV-683-3201 in bipolar disorder. Data from this study gives additional support to the proposed dose in PM patients (i.e. to reduce the dose by half) and indicates that no dose adjustment is needed in IM subjects.

This risk for increase of exposure of iloperidone and P88 based on genotype should be taken into account regarding the safety profile and the risk for QT prolongation – please refer to the Clinical safety section. The suggestion to reduce the posology in PM patients by half is in line with available data and is acceptable.

Of note, the applicant suggested a modification of posology if patients are genotyped as poor metabolisers, but genotyping is not generally used, may be problematic to implement in the target population and was also not proposed. There is a major concern that poor metabolizers will go undetected prior to dosing and will have a drug exposure significantly higher than extensive metabolizers, which may be linked to considerable safety concerns. See further discussion in Clinical safety section.

Dose proportionality and time dependency

For iloperidone, dose-proportionality was concluded in the dose range of 2 mg b.i.d. to 8 mg b.i.d. 12 mg b.i.d. is the highest dose suggested and shows a small deviation from dose proportionality. Dose proportionality is shown for P95 and P88 in the iloperidone dose range of 2 mg b.i.d. to 12 mg b.i.d.

Twice-daily dosing regimen resulted in a two-fold accumulation of iloperidone, and for P88 the observed accumulation was roughly 1.5-fold. 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. Thus, there are no signs of time-dependency.

Pharmacokinetics in the target population and therapeutic window

It can be concluded that the pharmacokinetics of healthy subjects and schizophrenic patients are comparable.

The therapeutic window of iloperidone is currently not clear. An additional complication is that there are metabolites contributing to efficacy and/or safety and an "active moiety" concept would need to be applied. P88 is considered an active metabolite that also causes a risk of QT prolongation. The potential activity of P95 is not entirely clear, but it may contribute to side effects although not to QT prolongation at clinically relevant concentrations. The main safety issue with iloperidone is the risk for QT prolongation; thus there is a need to reduce the dose in patients who are at risk of increased exposure of iloperidone and P88, e g for CYP2D6 poor metabolisers and due to drug-drug interactions. However, there is currently no request to genotype patients before start of treatment, and there is thus a risk of overdosing patients whose poor metaboliser status is unknown. On the other hand, genotyping may be problematic to implement in the target population.

Special populations

The Applicant claimed that renal impairment is unlikely to have a significant impact on the pharmacokinetics of iloperidone, due to a small proportion of the drug being excreted unchanged in the urine. However, subjects with severe renal impairment may also have a reduced hepatic elimination capacity as discussed in the Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with decreased renal function. Based on the performed RI study, severe renal impairment appeared to be associated with an up to 80% increase in Iloperidone exposure (expressed as $AUC_{0-\infty}$) and a 3-fold increase in P95 exposure, which suggest that P95 could accumulate upon chronic dosing of Iloperidone. As P95 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. Iloperidone should not be recommended in patients with severe renal impairment and should be used with caution in patients with moderate renal impairment. In the previous applications, given the uncertainties in very large, extrapolated areas and also issues with

erroneous classification of subjects to group of renal status, the applicant was recommended to perform a new study in patients with both moderate and severe renal impairment (with sufficiently long sampling to capture the majority of P95 exposure). The applicant committed to perform a new renal impairment study post-approval.

Iloperidone is primarily eliminated via hepatic metabolism. Hence, impaired hepatic function is expected to influence the pharmacokinetics of iloperidone and its metabolites. However, the exposure to total and free iloperidone remained unchanged in subjects with mild or moderate hepatic impairment compared to healthy individuals. Subjects with moderate hepatic impairment had a higher (about 2-fold) and more variable exposure to free P88. Since iloperidone has not been studied in patients with severe hepatic impairment, the proposed recommendation to not use it in this population is supported. It is also agreed that no dose adjustment is needed in patients with mild hepatic impairment. The applicant proposed that iloperidone should be used with caution in patients with moderate hepatic impairment, with careful titration based on clinical response and tolerability. A more actionable recommendation would have been preferred, but the current wording could be accepted.

Based on data presented from Study VP-VVV-683-3201, there does not appear to be a clinically relevant difference in exposure (Cmax,ss) with respect to gender or body weight.

A conclusion regarding the relationship between exposure and ethnicity cannot be drawn. A difference with respect to ethnicity, other than differences in occurrence of CYP2D6 metabolism profiles is not expected.

In the Clinical pharmacology summary, no PK data in the elderly are mentioned (and there is very limited experience from clinical studies of treatment of elderly patients). Except for effects due to renal or hepatic impairment, no different PK is expected in the elderly and no dosing adjustments for elderly was proposed by the applicant in the product information.

No paediatric indication is claimed. No data is available in the paediatric population.

Pharmacokinetic drug-drug interactions

Iloperidone and metabolites as victims of drug-drug interactions

CYP2D6 and CYP3A4 are involved in the metabolism of iloperidone, which is confirmed by the drug-drug interaction studies with CYP2D6 and CYP3A4 inhibitors resulting in higher systemic exposure leading to increased risk of QT prolongation and potential cardiotoxicity. The strong CYP3A4 inhibitor ketoconazole increased AUC and C_{max} of both iloperidone and P88 in CYP2D6 extensive metabolisers about 1.6-fold. The increase in exposure for P95 was somewhat lower (1.4-fold). The strong CYP2D6 inhibitor fluoxetine increased iloperidone exposure (AUC) 2.4 - fold and P88 2.2 – fold, while C_{max} increased about 1.7-fold for both substances. For P95, the exposure decreased upon co-administration with fluoxetine and was approximately 0.4-fold. Data on the effects of concomitant inhibition of CYP3A4 and CYP2D6 is available from the thorough QT study, but only effects on C_{max} were determined and effects on AUC are likely larger based on what was seen in the fluoxetine study. The strong CYP2D6 inhibitor paroxetine resulted in 1.6-1.7-fold increases in C_{max} for both iloperidone and P88 (consistent with the results from the fluoxetine study) and with combined administration of paroxetine and ketoconazole there was a 2.3-fold increase in in C_{max} for iloperidone and a 2.3-2.7-fold increase for P88 compared to administration without inhibitors. Paroxetine dosing up to 12 days is expected to be sufficient to reach a high level of CYP2D6 inhibition, so that the level of inhibition reached in the QT study would be expected to be representative of a poor CYP2D6 metaboliser administered a strong CYP3A4 inhibitor. It is however noted based on comparison to data from the pharmacogenetic sub-study of the thorough QT study that metabolic inhibition does not appear to evoke the same QT

prolongation potential as that observed in the (few) subjects genotyped by the applicant as CYP2D6 PMs.

There is a recommendation to reduce the dose by one-half with concomitant administration of a strong CYP3A4 or a strong CYP2D6 inhibitor. Regarding CYP2D6, this dose reduction would be expected to result in slightly higher exposure of iloperidone and P88 compared to giving the normal dose without a strong CYP2D6 inhibitor in CYP2D6 EMs. Regarding CYP3A4, this dose reduction would be expected to lead to a slightly lower exposure of iloperidone and P88 in CYP2D6 EMs compared to giving the normal dose without a strong CYP3A4 inhibitor, which may be adequate from a safety perspective in CYP2D6 EMs (although it is not entirely clear if efficacy would be affected).

In case of concomitant use with both a strong CYP3A4 and a strong CYP2D6 inhibitor, the SmPC recommends reducing the dose by "about one-half". It is not entirely clear how the recommendation regarding dose-reduction by "about one-half" should be implemented. Reducing the dose by half in patients treated concomitantly with a strong CYP3A4 inhibitor and a CYP2D6 inhibitor will still lead to an increased C_{max} of both iloperidone and P88, and likely an even more increased AUC, compared to giving the normal dose to patients without concomitant inhibitors. The same would be expected for a CYP2D6 PM subject given concomitant treatment with a strong CYP3A4 inhibitor.

Of particular note, there is also a recommendation to reduce the dose by 50% in (known) CYP2D6 PMs but there is currently no request according to the SmPC that patients should be genotyped before starting treatment with iloperidone. This is a critical issue considering the risk of QT prolongation which is further discussed in the Clinical safety part.

There are no clinical data with less potent CYP2D6 or CYP3A4 inhibitors and no monitoring was proposed or implemented by the applicant for those uses.

Thus, it has still not been sufficiently justified that the currently proposed dose adjustments in case of use with interacting drugs affecting the exposure of iloperidone and metabolites will result in effective and safe concentrations, considering the risks of QT prolongation. In particular, it has not been demonstrated that the dose reduction with strong CYP3A4 inhibitors would result in safe concentrations in patients who are CYP2D6 PMs or if the dose reduction is adequate in case of combining both a strong CYP3A4 inhibitor and a strong CYP2D6 inhibitor.

A study investigating the effects of iloperidone on the CYP2D6 substrate dextromethorphan was performed, which did not indicate clinically relevant CYP2D6 inhibition by iloperidone. The dose of iloperidone, 3 mg, is low and only single dosing was performed, which means that an interaction effect may have been underestimated. However, based on in vitro data there is no signal of clinically relevant inhibition of CYP2D6 by iloperidone or its metabolites; thus an in vivo study investigating these effects would not be needed based on in vitro data.

The applicant has committed to submit a new in vitro OATP1B1 and OATP1B3 substrate study for iloperidone using a relevant concentration span, taking into account the unbound C_{max} value of iloperidone of 0.0008 µM, as well as additional in vitro transporter studies for renal and hepatic transporters for P88 and P85, using a relevant concentration span taking into account the respective unbound C_{max} values. Until data is available, the uncertainty regarding a potential interaction with OATP inhibitors is adequately proposed in interactions part based on the information obtained in study XT148070, P95 is a substrate of OAT3.

Iloperidone has decreased solubility at higher pH values. The solubility at pH 6.0 can still be classified as high at pH 6 but is below the high solubility criteria at pH 7.0 (and likely also at pH 6.8). Since the solubility is still high at pH 6, antacids or H2-receptor antagonists are not expected to affect exposure. PPIs could in theory affect exposure, but dissolution data give some support that there is no large risk of a relevant effect. Thus, a relevant effect of drugs that increase gastric pH is not expected.

Iloperidone and metabolites as perpetrators of drug-drug interactions

Although the in vivo study with midazolam was not optimally designed in order to investigate induction effects and although the highest clinical dose was not used, it is considered adequate to conclude that there was a net effect of mild inhibition by iloperidone. This was adequately reflected in the proposed product information, with wordings regarding caution in case of co-administration with sensitive CYP3A4 substrates with narrow therapeutic index.

It is not possible to confirm absence of PXR induction based on the midazolam study, since there are in vitro signals of both inhibition and induction of CYP3A4. The *in vitro* CYP1A2 induction study was not performed in accordance with guideline requirements, so it is no possible to conclude on absence of CYP1A2 induction. The applicant has committed to submit *in vitro* CYP induction studies with CYP2C8, CYP2C9, CYP2C19 and CYP1A2. Until the results of these studies are available, the uncertainty regarding induction of these enzymes should be reflected in the product information.

There is an *in vitro* signal of *in vivo* relevant inhibition of intestinal P-gp. The Applicant has committed to perform a clinical DDI study with dabigatran etexilate in order to clarify if iloperidone is an in vivo relevant P-gp inhibitor. Until the results of this study are available, appropriate SmPC wordings should be included.

Relationship between plasma concentration and effect and safety

Concerning exposure-response, all analyses performed are mainly graphical explorations including some linear regression, i.e. no thorough population exposure-response modelling has been performed. Due to several technical limitations of the data and derived exposures for us in exposure-response analysis, any conclusions based on these analyses should be made with caution.

Pharmacodynamics

QTc prolongation is of primary concern with regard to the secondary pharmacology of iloperidone and its metabolites. The applicant conducted a concentration-QTcF assessment of measurements at 2 hours from the TQT-study at 2 hours. Metabolic inhibition further increased QT prolongation, particularly when both CYP3A4 and CYP2D6 pathways were inhibited (e.g., with ketoconazole and paroxetine). A key observation is that both iloperidone and its active metabolite P88 contribute to QT prolongation, with a statistically significant association between their concentrations and QT changes ($p < 0.01$ for iloperidone; $p < 0.02$ for P88). The results from the analysis support that iloperidone and P88 adversely affects the QT interval. To increase the understanding of the relationship between concentration and QTc, a concentrations-QT model-based analysis is requested (*please refer to section 2.6.8. Clinical Safety*).

A clarification of the qualitative and quantitative contribution of the P95 metabolite to the clinical effects of iloperidone in humans was requested, but there are remaining uncertainties regarding this topic. Since it appears that follow-up questions to the Applicant would not shed more light on the issue, it is not further pursued.

2.6.4. Conclusions on clinical pharmacology

The main safety issue with iloperidone is the risk for QT prolongation; thus there is a need to reduce the dose in patients who are at risk of increased exposure, e g for CYP2D6 poor metabolisers and due to drug-drug interactions. However, genotyping is not generally used, may be problematic to implement in the target population and is also not proposed in the current SmPC. There is a major concern that poor metabolizers will go undetected prior to dosing and will have a drug exposure significantly higher than extensive metabolizers, which may be linked to considerable safety concerns.

This is further discussed in the Clinical safety section. The reduction of the dose by one-half for poor metabolisers of CYP2D6 is reasonable based on available data. It has not been justified that the currently proposed dose adjustments in case of use with interacting drugs affecting the exposure of iloperidone and metabolites will result in effective and safe concentrations considering the risks of QT prolongation. In particular, it has not been demonstrated that the dose reduction with strong CYP3A4 inhibitors would result in safe concentrations in patients who are CYP2D6 PMs or if the dose reduction is adequate in case of combining both a strong CYP3A4 inhibitor and a strong CYP2D6 inhibitor. Reducing the dose by half in patients treated concomitantly with a strong CYP3A4 inhibitor and a CYP2D6 inhibitor will lead to a slightly increased C_{max} of both iloperidone and P88, and likely an even more increased AUC, compared to giving the normal dose to patients without concomitant inhibitors. The same would be expected for a CYP2D6 PM subject given concomitant treatment with a strong CYP3A4 inhibitor.

The popPK model is not considered adequate, but issues with the model are not pursued further.

The applicant has committed to submit several new *in vitro* studies as well as an *in vivo* P-gp inhibition study and an *in vivo* renal impairment study post-approval.

A clarification of the qualitative and quantitative contribution of the P95 metabolite to the clinical effects of iloperidone in humans was requested, but there are remaining uncertainties regarding this topic. Since it appears that follow-up questions to the Applicant would not shed more light on the issue, it was not further pursued.

2.6.5. Clinical efficacy

The dossier contained 11 placebo-controlled trials that had a primary or secondary efficacy endpoint and that CHMP considered relevant for the assessment of clinical efficacy in the proposed indications. All trials were randomised and double blind. The trials are summarised in the table below.

Table 9: Summary of the clinical trials that were considered relevant for the assessment of clinical efficacy

Study number	Phase	Population	Arms	Number of patients
VP-VYV-683-**3201**	3	Acute manic or mixed episodes associated with bipolar I disorder	Iloperidone 12-24 mg/d Placebo	417
ILO522 D**2301/** CILO522 D**2301**	3	Schizophrenia	Iloperidone 8-24 mg/d Placebo	303
ILP**2001**	2	schizophrenia or schizoaffective disorder	Iloperidone 12 mg/d Haloperidol 15 mg/d	120
ILP**3000**	3	Schizophrenia or schizoaffective disorder	Iloperidone 4 mg/d Iloperidone 8 mg/d Iloperidone 12 mg/d Haloperidol 15 mg/d Placebo	621
ILP**3001**	3	Schizophrenia or schizoaffective disorder	Iloperidone 4-16 mg/d Haloperidol 5-20 mg/d	600

ILP**3002**	3	Schizophrenia or schizoaffective disorder	Iloperidone 4-16 mg/d Haloperidol 5-20 mg/d	557
ILP**3003**	3	Schizophrenia or schizoaffective disorder	Iloperidone 4-16 mg/d Haloperidol 5-20 mg/d	487
ILP**3004**	3	Schizophrenia or schizoaffective disorder	Iloperidone 4- 8 mg/d Iloperidone 10-16 mg/d Risperidone 4-8 mg/d Placebo	616
ILP**3005**	3	Schizophrenia or schizoaffective disorder	Iloperidone 12-16 mg/d Iloperidone 20-24 mg/d Risperidone 6-8 mg/d Placebo	706
ILPB**202**	2	Schizophrenia	Iloperidone 4 or 8 mg/d Placebo	104
VP-VYV-683-**3101**	3	schizophrenia	Iloperidone 24 mg/d Ziprasidone 160 mg/d Placebo	606

2.6.5.1. Dose response study(ies)

No formal dose-response studies were performed prior to the phase 3 studies in schizophrenia, where doses between 4 mg and 24 mg/d were studied. The doses used in the bipolar study were chosen because they, according to the Applicant, were shown to be effective and safe based on the schizophrenia program.

2.6.5.2. Main study(ies)

The dossier contained 11 clinical trials that CHMP considered to be relevant for the assessment of clinical efficacy. Five of these trials (studies 3000, 3004, 3005, 3101, 2301) were considered to be main studies, and the reason for this is provided in the section *Discussion on clinical efficacy.* The methods and results of the 5 main studies are described below.

Study 3000: 6-week efficacy, fixed dose

Study title: A prospective, randomized, double-blind, placebo- and active-controlled, multicentre 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 double-blind, active-controlled, flexible-dose, long-term, 20-week phase with iloperidone (4, 8, 12, or 16 mg/d) given q.d.

Methods

- **Study Participants**

The study population consisted of patients with schizophrenia or schizoaffective disorder with acute or subacute exacerbation.

Main inclusion criteria:

- diagnosed with schizophrenia according to DSM-IV criteria. This included DSM-IV diagnosis of schizophrenia (i.e., 295) with suffixes 10 (disorganized), 20 (catatonic), 30 (paranoid), 60 (residual), 70 (schizoaffective), or 90 (undifferentiated);
- met Criterion A symptoms of the DSM-IV schizophrenia criteria for at least the 2 weeks prior to baseline.
- had PANSS Total (PANSS-T) score of at least 60;
- had a rating of at least "4" ("moderate") on at least 3 of the following 5 symptoms on the PANSS Positive Syndrome: delusions, conceptual disorganization, hallucinatory behaviour, grandiosity and suspiciousness/persecution.

Main exclusion criteria:

- met the DSM-IV criteria for schizophreniform disorder (295.40) or met any other primary psychiatric diagnosis (Axis I) according to DSM-IV criteria.
- had a diagnosis or history suggestive of chemical dependence, according to DSM-IV criteria, or toxic psychosis in the preceding 6 months, or a clinical presentation possibly confounded by the use of recreational drugs or alcohol.
- had other medical conditions that could be expected to progress, recur, or change to such an extent that they may put the patient at special risk or bias the assessment of the clinical and the mental status of the patient to a significant degree (e.g., second degree or higher heart block, severe or deteriorating cardiovascular disease, clinically relevant ECG abnormality, severe obstructive lung disease, untreated thyroid disease, myocardial infarction within the past 6 months, insulin-dependent diabetes). This included any nonpsychiatric coexistent disease state that had not been maintained in a stable condition for at least 3 months prior to baseline.

Patients who consented to participate in the study agreed to be hospitalized for at least 10 days (i.e., during the placebo run-in and the titration period of the initial double-blind phase) and at any other time throughout the study, if medically necessary.

- **Treatments**

The study consisted of a screening phase of four weeks, a single-blind placebo run in period of two days followed by a double-blind, placebo- and haloperidol-controlled period of 42 days. The doses of iloperidone and haloperidol were titrated as shown in Table 10. Patients who consented to participate in the study agreed to be hospitalized for at least 10 days (i.e., during the placebo run-in and the titration period of the initial double-blind phase) and at any other time throughout the study, if medically necessary.

Table 10: Study 3000, study schema

Pre-randomization phase		Initial double-blind phase (b.i.d. dosing)	
Screening	Single-blind placebo run-in	Titration period (fixed dose increases every other day until the target dose was reached)	Maintenance period (fixed doses)
Days -30 to –3	Days –2 to 0	Days 1 to 7	Days 8 to 42
		Ilo: 2→4 mg/d	Ilo: 4 mg/d
		Ilo: 2→4→8 mg/d	Ilo: 8 mg/d

Screening visit	Pbo (b.i.d. dosing)	Ilo: 2→4→8→12 mg/d	Ilo: 12 mg/d
		Hal: 2→5→10→15 mg/d	Hal: 15 mg/d
		Pbo	Pbo

Ilo=iloperidone; Hal=haloperidol; Pbo=Placebo

No standardised criteria for treatment rescue were defined. Rescue medication was used at the investigator's discretion. *Insomnia* was treated with chloral hydrate or zolpidem, *agitation/severe restlessness* was treated with chloral hydrate, lorazepam or sodium amytal and *EPS* were treated with benztropine.

- **Objectives**

The primary objective was to determine the efficacy and safety of iloperidone 4, 8 and 12 mg/d (administered as 2, 4 and 6 mg b.i.d.) and haloperidol 15 mg/d (7.5 mg b.i.d.) compared with that of placebo over 42 days in schizoaffective or schizophrenic patients with acute or subacute exacerbation.

The secondary comparisons of interest included each of the iloperidone 8mg/d and 12 mg/d doses versus placebo. Additionally, iloperidone 4 mg/d was compared with placebo.

- **Outcomes/endpoints**

The primary efficacy endpoint for this study was the change from baseline to end of study (Day 42 or premature discontinuation) on the PANSS-T score in the LOCF dataset. In the primary efficacy analysis, the primary treatment comparison was the average of iloperidone 8 and 12mg/d treatment groups versus placebo.

The secondary efficacy endpoints were:

• The change from baseline to each post-baseline assessment on the PANSS-T score, the scores of the PANSS subscales (i.e., PANSS-P, PANSS-N and PANSS-GP), the PANSS-derived 18-item BPRS and the CDS score.

• The proportion of patients achieving a 20% or greater reduction from baseline on the PANSS-T score, the scores of the three PANSS subscales, the PANSS-derived 18-item BPRS and the CDS score.

• The proportion of patients reaching clinical improvement (defined as minimally, much, or very much improved on the CGI-C) at each time point. The analysis of the CGI-C data was based on the dichotomization of the CGI-C to indicate improvement (minimally, much, or very much improved) versus no improvement (no change, minimally, much, or very much worse).

- **Sample size**

The sample size calculation was based on detecting a delta = 8 for the total PANSS, with standard deviation (SD) = 22. The delta and SD were based on data from SDZ MAR 327 Study B104 comparing haloperidol and placebo. A total of 120 patients per arm was needed in order to have 80% power to show that an iloperidone dose group is significantly superior to placebo based on a two-sided t-test at alpha = 0.05 level.

- **Randomisation and Blinding (masking)**

Patients qualified for admission were randomized to treatment groups by the IVRS. The IVRS was also used to maintain the blind by assigning study medication to patients throughout the study.

The placebo run-in period used a single-blind design. The Investigator knew that all patients were receiving placebo, but patients did not know what study medication they were receiving.

During the initial double-blind phase, the Investigator, patient, and Sponsor were blinded to the drug identification and drug dose of each patient. During the long-term double-blind phase, the Investigator was blinded to the drug identification but was unblinded to the dose level (Level A, B, C, or D) of each patient. Patients were blinded to both the drug identification and dose level during the long-term double-blind phase.

- **Statistical methods**

Analysis sets and missing data

The intent-to-treat (ITT) population included all randomised patients who received at least one dose of double-blind study medication and from whom at least one post-baseline efficacy measurement was obtained. The efficacy analysis was based on the ITT population. Efficacy measurements made more than 3 days beyond the last day study medication was administered were not included in the summary analyses.

The following two data-handling approaches were used for each scheduled post-baseline visit in the efficacy analyses:

Last observation carried forward (LOCF) - If a patient had a missing evaluation for a visit, the immediately preceding non-missing evaluation was used as the value for that visit. This imputation scheme ensured that an observation was available for analysis at each scheduled visit for every ITT patient. The primary efficacy evaluation was based on the LOCF dataset.

Observed cases (OC) - If a patient had a missing evaluation for a visit, it was left missing. The OC analysis, therefore, included only the data observed during the study from all ITT patients. In this dataset, therefore, no imputation scheme was used.

Statistical analysis

In the primary efficacy analysis, the pre-specified primary treatment comparison was the average of iloperidone 8 and 12mg/d treatment groups versus placebo. The secondary comparisons of interest included each of the iloperidone 8mg/d and 12 mg/d doses versus placebo. Additionally, iloperidone 4 mg/d was compared with placebo.

A two-way analysis of covariance (ANCOVA) model was used for the analysis of treatment main effect on continuous variables. The terms in the model included treatment, centre, baseline (as covariate), and the treatment-by-baseline term.

An additional analysis was performed for the exploration of treatment-by-centre interaction by adding this interaction term to the above ANCOVA model. If a treatment-by-centre interaction was detected, the interaction was explored in an ad-hoc manner.

Categorical variables were analysed using Cochran-Mantel-Haenszel (CMH) test blocking on centres.

Interim analysis

No interim analysis was planned or performed.

Results

- **Participant flow**

Table 11: Patient disposition, by treatment. Study 3000. All randomized patients

Treatment group	Ilo 4 mg/d		Ilo 8 mg/d		Ilo 12 mg/d		Ilo all		Hal 15 mg/d		Pbo		Total	
	N=121		N=125		N=124		N=370		N=124		N=127		N=621	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Completed Day 42	52	(43)	45	(36)	52	(42)	149	(40)	43	(35)	40	(31)	232	(37)
Discontinued (Never received double-blind study medication)[a]	0	(0)	2	(2)	1	(1)	3	(1)	5	(4)	0	(0)	8	(1)
Discontinued (Days 1-42)	69	(57)	80	(64)	72	(58)	221	(60)	81	(65)	87	(69)	389	(63)
Primary[b] reason for discontinuation (Days 1-42)														
Adverse experiences	6	(5)	12	(10)	7	(6)	25	(7)	11	(9)	8	(6)	44	(7)
Adverse events (AEs)	6	(5)	12	(10)	7	(6)	25	(7)	11	(9)	7	(6)	43	(7)
Treatment emergent AEs	5	(4)	10	(8)	7	(6)	22	(6)	9	(7)	7	(6)	38	(6)
Not treatment emergent AEs [c]	1	(1)	2	2(2)	0	(0)	3	(1)	2	(2)	0	(0)	5	(1)
Abnormal test procedure[d]	0	(0)	0	0(0)	0	(0)	0	(0)	0	(0)	1	(1)	1	(0)
Unsatisfactory therapeutic effect	36	(30)	38	(30)	36	(29)	110	(30)	31	(25)	44	(35)	185	(30)
Protocol violation	1	(1)	2	(2)	3	(2)	6	(2)	4	(3)	1	(1)	11	(2)
Withdrawal of consent	18	(15)	21	(17)	22	(18)	61	(16)	29	(23)	26	(20)	116	(19)
Lost to follow-up	6	(5)	5	(4)	2	(2)	13	(4)	6	(5)	5	(4)	24	(4)
Administrative problems	2	(2)	2	(2)	2	(2)	6	(2)	0	(0)	3	(2)	9	(1)

- **Recruitment**

First patient recruited: 24 Oct 1998. Last patient completed: 17 Aug 1999.

- **Conduct of the study**

There were no protocol amendments that affected the main efficacy results.

- **Baseline data**

Baseline data is presented in Table 12 and Figure 3.

Table 12: Study 3000. Demographic and background information, by treatment. All randomized patients

Treatment	Ilo 4 mg/d N=121	Ilo 8 mg/d N=125	Ilo 12 mg/d N=124	Hal 15 mg/d N=124	Pbo N=127
Age (years)	38.4	37.0	40.1	39.1	39.3
Sex n (%)					
Male	82 (68)	94 (75)	91 (73)	85 (69)	90 (71)
Female	39 (32)	31 (25)	33 (27)	39 (31)	37 (29)
Race n (%)					
Caucasian	57 (47)	49 (39)	67 (54)	58 (47)	64 (50)
Black	52 (43)	58 (46)	44 (35)	54 (44)	55 (43)
Oriental	2 (2)	1 (1)	2 (2)	3 (2)	0
Other	10 (8)	17 (14)	11 (9)	9 (7)	8 (6)
DSM-IV criteria n (%)					
Class'n of schizophrenia	89 (74)	87 (69)	89 (72)	78(63)	84 (66
Class'n of schizoaffective	32 (26)	37 (30)	35 (28)	46 (37)	43 (34)
Missing	0	1 (1)	0	0	0

Ilo=iloperidone; Hal=haloperidol; Pbo=placebo

Figure 3: Study 3000. Age psychosis diagnosed

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Post-text Table 7.4-1
Demographic and background information: By treatment
Initial double-blind phase (Days 1-42)
All randomized patients

		Ilo 4 mg N=121		Ilo 8 mg N=125		Ilo 12 mg N=124		Hal N=124		Pbo N=127		Total N=621	
Race	Caucasian	57	(47)	49	(39)	67	(54)	58	(47)	64	(50)	295	(48)
	Black	52	(43)	58	(46)	44	(35)	54	(44)	55	(43)	263	(42)
	Oriental	2	(2)	1	(1)	2	(2)	3	(2)	0		8	(1)
	Other	10	(8)	17	(14)	11	(9)	9	(7)	8	(6)	55	(9)
Age psychosis	N	118		122		122		121		123		606	
diagnosed (years)	Mean	23.8		22.4		23.1		23.1		23.6		23.2	
	SD	9.6		7.1		7.9		6.9		8.3		8.0	
	Median	22.0		20.0		21.5		21.0		21.0		21.0	
	Minimum	3		9		6		11		6		3	
	Maximum	57		42		54		45		56		57	
Age psychosis	<18	30	(25)	29	(23)	27	(22)	23	(19)	22	(17)	131	(21)
diagnosed (years)	18-24	42	(35)	53	(42)	51	(41)	58	(47)	55	(43)	259	(42)
	25-44	44	(36)	40	(32)	42	(34)	39	(31)	42	(33)	207	(33)
	45-65	2	(2)	0		2	(2)	1	(1)	4	(3)	9	(1)
	Missing	3	(2)	3	(2)	2	(2)	3	(2)	4	(3)	15	(2)

- **Numbers analysed**

See Table 11.

- **Outcomes and estimation**

Primary outcome: The average of iloperidone 8 and 12 mg/d iloperidone treatment groups did not show a significantly greater reduction on the PANSS-T than the placebo group at Week 6, see Table 13.

Secondary outcomes:

The change from baseline to each post-baseline assessment on the PANSS-T score: In the LOCF dataset, the iloperidone 12 mg/d group demonstrated a statistically significantly greater reduction compared with placebo in the PANSS-T score at Weeks 4 and 6, see Table 13. The haloperidol group showed statistically significantly greater reduction in the PANSS-T score compared with placebo from Weeks 2 through 4.

Mean change from baseline for CDS: No statistically significant difference from the placebo group was detected for any of the iloperidone groups.

The proportion of patients achieving a 20% or greater reduction from baseline on the PANSS-T score: For the iloperidone groups, the proportion of patients who achieved ≥20% reduction relative to baseline on the PANSS-T was not statistically significantly different from placebo, see Table 14.

The proportion of patients with clinical improvement in the CGI-C: Compared with placebo, the proportion of patients reaching clinical improvement on the CGI-C was statistically significant in the iloperidone 8 mg/d group at Weeks 4 and 6 and in the 12 mg/d group at Week 4. For the haloperidol group, a statistically significant proportion of patients achieved clinical improvement compared with placebo from Week 4.

Table 13: Study 3000. PANSS-Total score Change from baseline. Intent-to-treat population - Last observation carried forward

Visit		Ilo 4 mg	Ilo 8 mg	Ilo 12 mg	Hal	Pbo	Ilo 4 mg vs Pbo	Ilo 8 mg vs Pbo	Ilo 12 mg vs Pbo	Hal vs Pbo	Ilo (8mg+12mg)/2 vs Pbo **
							P values for Pairwise Comparisons+				
Week 1	N	113	114	115	114	117	0.710	0.928	0.646	0.120	0.751
	BSL Mean (SD)	95.0 (15.3)	95.7 (15.9)	94.6 (14.8)	96.1 (15.6)	95.0 (17.0)					
	Mean Change	2.3	2.7	3.8	5.8	3.0					
	Change SD	14.4	13.6	15.5	15.9	17.2					
Week 2	N	113	114	115	114	117	0.936	0.335	0.387	<0.001*	0.291
	Mean Change	3.6	5.4	5.4	11.1	3.5					
	Change SD	16.0	16.7	16.2	17.4	19.9					
Week 3	N	113	114	115	114	117	0.259	0.238	0.098	<0.001*	0.102
	Mean Change	5.6	5.5	7.0	11.1	3.4					
	Change SD	17.1	18.1	17.7	18.4	22.4					
Week 4	N	113	114	115	114	117	0.124	0.277	0.015*	<0.001*	0.043*
	Mean Change	6.5	5.1	8.7	12.0	3.1					
	Change SD	20.4	18.8	20.0	20.0	22.7					
Week 5	N	113	114	115	114	117	0.146	0.466	0.065	<0.001*	0.137
	Mean Change	7.3	5.2	8.2	11.9	4.1					
	Change SD	21.5	19.3	19.4	20.3	23.0					
Week 6	N	113	114	115	114	117	0.097	0.227	0.047*	<0.001*	0.065
	Mean Change	7.8	6.4	8.6	12.5	4.1					
	Change SD	22.2	20.2	19.6	21.3	24.1					

Ilo=iloperidone; Hal=haloperidol; Pbo=placebo

Table 14: Study 3000. PANSS total score; percent patients with ≥20% improvement. Intent-to-treat population - Last observation carried forward

	Ilo 4 mg		Ilo 8 mg		Ilo 12 mg		Hal		Pbo		Ilo 4 mg vs Pbo	Ilo 8 mg vs Pbo	Ilo 12 mg vs Pbo	Hal vs Pbo
Visit	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)				
Week 1	113	20(18)	114	23(20)	115	30(26)	114	32(28)	117	30(26)	0.070	0.246	0.815	0.434
Week 2	113	29 (26)	114	33 (29)	115	31 (27)	114	57 (50)	117	38 (32)	0.205	0.468	0.296	0.011*
Week 3	113	40 (35)	114	37 (32)	115	41 (36)	114	57 (50)	117	35 (30)	0.426	0.543	0.308	0.001*
Week 4	113	43 (38)	114	40 (35)	115	49 (43)	114	54 (47)	117	37 (32)	0.462	0.545	0.084	0.012*
Week 5	113	47 (42)	114	38 (33)	115	45 (39)	114	51 (45)	117	38 (32)	0.184	0.721	0.256	0.049*
Week 6	113	45 (40)	114	39 (34)	115	49 (43)	114	54 (47)	117	39 (33)	0.327	0.737	0.091	0.021*

Ilo=iloperidone; Hal=haloperidol; Pbo=placebo

- **Ancillary analyses**

The Applicant provided post-hoc analyses of treatment response defined as at least 30% and at least 40% reduction on the total PANSS score compared to baseline, in schizophrenia patients only. No (nominally) statistically significant difference was found on the PANSS-T between any of the iloperidone treatment groups and placebo in these analyses. In the haloperidol treatment group, 17.1% of patients had at least 30% reduction of the PANSS score from baseline from treatment weeks 4 through 6. Nominal statistical significance compared to placebo was shown in week 4.

Study 3004: 6-week efficacy, dose range

Study title: A randomized, double-blind, placebo- and risperidone-controlled, multicentre study to evaluate the efficacy and safety of two nonoverlapping 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.

Methods

This was a prospective, randomized, double-blind, placebo- and risperidone-controlled, phase-3 multicentre study evaluating two non-overlapping dose ranges of iloperidone given b.i.d. for 42 days to schizophrenic patients with acute or subacute exacerbation.

Study Participants

The patient population for this study included patients with schizophrenia or schizoaffective disorder with acute or subacute exacerbation.

Main inclusion criteria:

- diagnosed with schizophrenia according to DSM-IV criteria. This included DSM-IV diagnosis of schizophrenia (i.e., 295) with suffixes 10 (disorganized), 20 (catatonic), 30 (paranoid), 60 (residual), 70 (schizoaffective), or 90 (undifferentiated).
- met Criterion A symptoms of the DSM-IV schizophrenia criteria for at least the 2 weeks prior to baseline.
- had PANSS Total (PANSS-T) score of at least 60 at screening and baseline.
- had a rating of at least "4" ("moderate") on at least 3 of the following 5 symptoms on the PANSS positive syndrome scale: delusions, conceptual disorganization, hallucinatory behaviour, grandiosity, and suspiciousness/persecution.

Main exclusion criteria:

- met the DSM-IV criteria for schizophreniform disorder (295.40) or met any other primary psychiatric diagnosis (Axis I) according to DSM-IV criteria.
- had a diagnosis or history suggestive of chemical dependence, according to DSM-IV criteria, or toxic psychosis in the preceding 6 months, or a clinical presentation possibly confounded by the use of recreational drugs or alcohol.
- had other medical conditions that could be expected to progress, recur, or change to such an extent that they may put the patient at special risk or bias the assessment of the clinical and the mental status of the patient to a significant degree (e.g., second degree or higher heart block, severe

or deteriorating cardiovascular disease, clinically relevant ECG abnormality, severe obstructive lung disease, untreated thyroid disease, known human immunodeficiency virus or Hepatitis C infection, myocardial infarction within the past 6 months, insulin-dependent diabetes). This included any nonpsychiatric coexistent disease state that had not been maintained in a stable condition for at least 3 months prior to baseline.

Treatments

Two non-overlapping dose ranges of iloperidone (4-8 mg/d and 10-16 mg/d) were used. Risperidone was used as the active reference therapy. During the titration period (Days 1-7), fixed-dosing regimens were used whereby doses were increased up to pre-assigned target doses. Although patients in different treatment groups reached their target doses on different days, the titration period for all treatment groups covered the first 7 days for study design purposes. In the maintenance period, flexible dosing regimens were used whereby patients were maintained within pre-assigned target dose ranges from Days 8-42. See Table 15.

Patients who consented to participate in the study agreed to be hospitalized for at least 10 days (i.e., during the placebo run-in period and the titration period of the initial double-blind phase) and at any other time throughout the study, if medically indicated.

Table 15: Study 3004, study schema

Pre-randomization phase		Initial double-blind phase (b.i.d. dosing)	
Screening	Single-blind placebo run-in	Fixed titration	Flexible maintenance
Days -30 to -3	Days –2 to 0 [a]	Days 1 to 7	Days 8 to 42
No study medication	Pbo (b.i.d. dosing)	Ilo low: 2→4→6 mg/d	Ilo 4, 6,[b] or 8 mg/d
		Ilo high: 2→4→8→12 mg/d	Ilo: 10, 12,[b] or 16 mg/d
		Ris: 2→4→6 mg/d	Ris: 4, 6,[b] or 8 mg/d
		Pbo	Pbo

Abbreviations: Pbo=placebo; ILO=iloperidone; RIS=risperidone; mg/d=milligrams/day; b.i.d.=twice daily
a The placebo run-in period lasted 3 days. The last day of placebo run-in period is baseline (Day 0).
b Titration target dose

No standardised criteria for treatment rescue were defined. Rescue medication was used at the investigator's discretion. *Insomnia* was treated with chloral hydrate or zolpidem, *agitation/severe restlessness* was treated with chloral hydrate, lorazepam or sodium amytal and *EPS* were treated with benztropine.

Objectives

The objective of the initial double-blind phase was to evaluate the efficacy and safety of two non-overlapping dose ranges of iloperidone (4-8 mg/d and 10-16 mg/d) and risperidone (4-8 mg/d) compared with placebo, over 42 days in patients with an acute or subacute exacerbation of schizophrenia or schizoaffective disorder.

Outcomes/endpoints

The primary efficacy endpoint for this study was the change from baseline to end of study (Day 42 or premature discontinuation) on the 18-item PANSS-derived BPRS score in the LOCF dataset. The primary treatment comparison was between the iloperidone 10-16 mg/d group and the placebo group, and between the iloperidone 4-8 mg/d group and placebo if the iloperidone 10-16 mg/d comparison with placebo was statistically significant.

The secondary efficacy endpoints were

- Change from baseline to each post-baseline assessment on the PANSS total score (PANSS-T), and the scores of the three PANSS subscales, and the BPRS.
- The proportion of patients who achieved a 20% or greater reduction on the PANSS-T score, and on the scores of the three PANSS subscales, and the 18-item PANSS-derived BPRS.
- The proportion of patients who were rated as minimally, much, or very much improved on the CGI-C at each time point.
- The mean change from baseline in the CGI-S at each time point.

Sample size

Initially, the sample size calculation was based on detecting a delta = 8 for the total PANSS, with standard deviation (SD) = 22. The delta and SD were based on data from SDZ MAR 327 Study B104 comparing haloperidol and placebo. A total of 150 patients per arm was needed in order to have 80% power to show that an iloperidone dose group is significantly superior to placebo based on a two-sided t-test at alpha = 0.025 level, where alpha = 0.025 was chosen to control the 0.05 familywise type-I error of the two multiple comparisons (that is, each of the two dose iloperidone groups versus placebo).

The sample size calculation was updated in Protocol Amendment No. 2 (dated 30-Nov-1999), when the primary endpoint was changed from total PANSS to the 18-item PANSS-derived BPRS. The standard deviation was assumed to be 12 based on data from iloperidone Study ILP3000, which compared a fixed dose of iloperidone 12 mg/d with placebo. A sample size of 150 patients per arm allowed detection of a ~4 point difference between iloperidone and placebo with 80% power and with a two-sided alpha=0.05.

Randomisation and blinding (masking)

Patients qualified for admission were randomised to treatment groups by the IVRS. The randomisation schedule was computer generated. One electronic copy was loaded into the IVRS. The IVRS was also used to maintain the blind by assigning study medication to patients throughout the study.

Single-blind study medication (placebo) was used during the placebo run-in period, and all double-blind study medication (iloperidone, risperidone, and placebo) were identical in appearance (i.e., size, colour, shape).

Sponsor personnel involved in the monitoring and conduct of the study and all study site personnel and patients were blinded to treatment during the initial double-blind phase. Once the initial double-blind phase of the study was completed and the database locked, site personnel and site monitors remained blinded to the patient's treatment group. Only those Sponsor/CRO employees involved in the analysis of the data and the preparation of the study report for the initial double-blind phase were unblinded. All study site personnel and patients remained blinded to treatment until results from the long-term double-blind phase were reported.

Statistical methods

Analysis sets and missing data

The intent to treat (ITT) population contained all randomised patients who receive at least one dose of double-blind study medication and from whom at least one efficacy measurement was obtained while on study medication. The efficacy analysis was based on the ITT population. Evaluations performed more than 3 days after the last double-blind study medication was taken were not included in the statistical analyses.

The following two data handling schemes were used for each scheduled post-baseline visit for the ITT population:

Last observation carried forward (LOCF) The goal of this imputation scheme was to create an observation for each scheduled visit for every ITT patient. If a patient had a missing evaluation for a visit, then the immediately preceding non-missing evaluation was used.

Observed cases (OC) In this data set, no imputation was used. It included only the data observed during the study from all ITT patients.

Efficacy analysis

The primary treatment comparison was changed during the study. Initially, the two iloperidone dose range groups were to be compared to placebo, and Hochberg's procedure was to be used to control the familywise Type-I error of the two comparisons. However, as of Protocol Amendment No. 2 (dated 30 November 1999), 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 also be tested at the 0.05 level. If the comparison of iloperidone 10-16 mg/d group with placebo was not significant, comparison of the iloperidone 4-8 mg/d group with placebo was not considered significant, regardless of the nominal significance level.

A two-way analysis of covariance (ANCOVA) model was used for the analysis of treatment main effect of continuous variables. The terms in the model included treatment, centre, baseline (as covariate), and the treatment-by-baseline term.

An additional analysis was performed for the exploration of treatment-by-centre interaction by adding this interaction term to the above ANCOVA model. If a treatment-by-centre interaction was detected, the interaction was explored in an ad-hoc manner.

Categorical variables were analysed using Cochran-Mantel-Haenszel (CMH) test blocking on centres.

Interim analysis

No interim analyses were planned or conducted.

Results

Participant flow

Table 16: Study 3004. Patient disposition, by treatment. All randomized patients

	Ilo 4-8 mg/d N=153 n(%)	Ilo 10-16 mg/d N=154 n(%)	Ris 4-8 mg/d N=153 n(%)	Pbo N=156 n(%)	Total N=616 n(%)
Discontinued days 1-42[a]	79 (52)	67 (44)	64 (42)	94 (60)	304(49)
Primary reason[b] for discontinuation					
Adverse experiences	5 (3)	6 (4)	12 (8)	11 (7)	34 (6)
Treatment emergent adverse event	3 (2)	6 (4)	9 (6)	10 (6)	28 (5)
Not treatment emergent adverse event[c]	2 (1)	0	3 (2)	1 (1)	6 (1)
Unsatisfactory therapeutic effect	36 (24)	33 (21)	24 (16)	64 (41)	157(25)
Protocol violation	3 (2)	3 (2)	1 (1)	0	7 (1)
Withdrawal of consent	28 (18)	21 (14)	12 (8)	14 (9)	75 (12)
Lost to follow-up	7 (5)	4 (3)	14 (9)	5 (3)	30 (5)
Death[d]	0	0	1 (0.6)	0	1 (0.2)

N=total number of patients; n=number of patients within the listed category; Ilo=iloperidone; Ris=risperidone; Pbo=placebo
[a] One patient from the placebo treatment group was randomized but was never dosed and for whom a phase completion CRF was not completed.
[b] Primary reason, as determined by the Investigator. Only one reason was recorded on Case Report Form.
[c] Includes patients who never received double-blind study medication.
[d] For one patient in the risperidone group the primary reason for discontinuation was death, although this patient also was considered to have had AEs resulting in discontinuation.

Recruitment

First patient recruited: 23-Jun-1999. Last patient completed: 11-May-2000.

Conduct of the study

While the study was ongoing, the primary endpoint was changed from the PANSS total score to the 18-item PANSS-derived BPRS because the results of Study 3000 indicated that the BPRS might be more sensitive in assessing treatment effects (protocol amendment 2, dated 30-Nov-1999).

Baseline data

Baseline data is presented in Table 17.

Table 17: Study 3004. Demographic and background characteristics, by treatment. All randomized patients

	Ilo 4 - 8 mg/d N=153	Ilo 10 - 16 mg/d N=154	Ris 4-8 mg/d N=153	Pbo N=156	Total N=616
Age (yr)					
Mean ± SD	38.4 ± 10.7	39.3 ± 10.1	37.5 ± 11.8	38.8 ± 10.5	38.5 ± 10.8
Median	40.0	39.0	37.0	39.0	39.0
Range	19 – 64	18 - 66	17 - 67	19 - 66	17 - 67
Age (yr) n (%)					
<18	0	0	2 (1)	0	2 (0)
18-24	19 (12)	10 (6)	24 (16)	14 (9)	67 (11)
25-44	87 (57)	99 (64)	84 (55)	91 (58)	361 (59)
45-65	47 (31)	44 (29)	42 (27)	50 (32)	183 (30)
>65	0	1 (1)	1 (1)	1 (1)	3 (0)
Sex - n(%)					
Male	105 (69)	109 (71)	115 (75)	104 (67)	433 (70)
Female	48 (31)	45 (29)	38 (25)	52 (33)	183 (30)
Race - n(%)					
Caucasian	92 (60)	91 (59)	92 (60)	89 (57)	364 (59)
Black	53 (35)	48 (31)	50 (33)	53 (34)	204 (33)
Oriental	5 (3)	7 (5)	1 (1)	2 (1)	15 (2)
Other	3 (2)	8 (5)	10 (7)	12 (8)	33 (5)
DSM-IV schizophrenia diagnosis					
295.10 disorganized	19 (12)	8 (5)	11 (7)	9 (6)	47 (8)
295.30 paranoid	81 (53)	87 (56)	83 (54)	90 (58)	341 (55)
295.70 schizoaffective	30 (20)	29 (19)	38 (25)	37 (24)	134 (22)
295.90 undifferentiated	23 (15)	30 (19)	21 (14)	20 (13)	94 (15)

Ilo=iloperidone; Ris=risperidone; Pbo=placebo

Numbers analysed

See Table 16.

Outcomes and estimation

Primary outcome: For the LOCF dataset, there was a statistically significant reduction in the 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), see Table 18.

Table 18: Study 3004. Positive and Negative Syndrome Scale (PANSS)- 18-item Brief Psychiatric Rating Scale (BPRS) score Change from baseline. Intent-to-treat population - Last observation carried forward

Visit		Ilo 4-8 mg	Ilo 10-16 mg	Ris	Pbo	Ilo 4-8 mg vs Pbo	Ilo 10-16 mg vs Pbo	Ris vs Pbo
						P values for Pairwise Comparisons+		
Week 1	N	143	149	146	152			
	BSL Mean (SD)	54.9 (8.8)	54.1 (9.1)	54.7(10.0)	54.2 (9.8)			
	Mean Change	3.9	3.4	5.7	2.8	0.411	0.546	0.018*
	Change SD	9.6	9.1	10.2	10.8			
Week 2	Mean Change	4.8	5.3	8.1	3.8	0.529	0.232	0.001*
	Change SD	10.0	10.4	12.4	12.2			
Week 3	Mean Change	5.1	6.5	9.0	2.9	0.190	0.009*	<0.001*
	Change SD	11.0	11.4	12.6	12.9			
Week 4	Mean Change	6.1	6.8	10.7	2.8	0.050*	0.005*	<0.001*
	Change SD	11.9	11.7	13.3	13.6			
Week 5	Mean Change	6.5	7.0	10.9	2.2	0.005*	0.001*	<0.001*
	Change SD	12.1	12.0	13.3	14.2			
Week 6	Mean Change	6.7	7.6	11.1	2.7	0.012*	0.001*	<0.001*
	Change SD	12.4	12.6	13.6	14.3			

Ilo=iloperidone; Ris=risperidone; Pbo=placebo

Secondary outcome: The proportion of patients with improvement (as defined by ≥ 20% reduction in the baseline BPRS score) increased over time in both iloperidone groups and the risperidone group. In the LOCF dataset, significant differences from placebo in the proportion of patients who improved, were not observed for either of the iloperidone groups. Compared to placebo, in the risperidone group, there were statistically significantly higher proportions of patients fulfilling this definition of improvement from Weeks 2 through 6, see Table 19.

Table 19: Study 3004. 18-item BPRS score, percent patients with ≥20% improvement. Intent-to-treat population - Last observation carried forward

	Ilo 4-8 mg		Ilo 10-16 mg		Ris		Pbo		Ilo 4-8 mg vs Pbo	Ilo 10-16 mg vs Pbo	Ris vs Pbo
Visit	N	n(%)	N	n(%)	N	n(%)	N	n(%)	P values for Pairwise Comparisons+		
Week 1	143	39 (27)	149	47 (32)	146	49 (34)	152	47 (31)	0.409	0.935	0.567
Week 2	143	51 (36)	149	60 (40)	146	77 (53)	152	63 (41)	0.174	0.553	0.045*
Week 3	143	55 (38)	149	72 (48)	146	80 (55)	152	59 (39)	0.763	0.191	0.007*
Week 4	143	64 (45)	149	74 (50)	146	85 (58)	152	58 (38)	0.375	0.058	0.001*
Week 5	143	67 (47)	149	72 (48)	146	88 (60)	152	57 (38)	0.128	0.098	<0.001*
Week 6	143	69 (48)	149	78 (52)	146	89 (61)	152	64 (42)	0.295	0.164	0.002*

Ilo=iloperidone; Ris=risperidone; Pbo=placebo. BPRS=18-item Brief Psychiatric Rating Scale score.

In the LOCF dataset, the proportions of patients who were improved (defined as minimally, much, or very much improved) on the CGI-C at week 6 was 54% in the Ilo 4-8 mg/d group, 58% in the Ilo 10-16 mg/d group and 43% in the placebo group, nominal p-value <0.05 for both Ilo treatment groups. This nominally significant difference between the Ilo treatment groups and placebo was seen from week 4. In the risperidone group, the proportion of patients who improved was nominally significantly greater than in the placebo group from week 1 through 6, 60 – 67% vs 46-43%, respectively.

Ancillary analyses

The Applicant provided post-hoc analyses of treatment response defined as at least 30% and at least 40% reduction on the 18-item BPRS score compared to baseline, in schizophrenia patients only.

No nominally statistically significant differences in favour of iloperidone treatment were demonstrated in any of the treatment groups compared to placebo regarding the proportion of responders, neither with 30% improvement nor with 40% improvement.

In the risperidone treatment group, 24.5 % of patients had at least 30% reduction of the PANSS score from baseline at treatment week 6 compared to 12.9% in the placebo group (nominal p 0.035). Corresponding figures for iloperidone was 16.5% in the 4-8 mg group and 20.7% in the 10-16 mg group, nominal p-value 0.357 and 0.180, respectively.

In the Ilo 10-16 mg/d group, 7.4% of patients had at least 40% reduction of the PANSS score from baseline at treatment week 6 compared to 6.0% in the placebo group (nominal p-value 0.945). Corresponding figures for the Ilo 4-8 mg/d group and the risperidone group was 5.2% and 16.4%, nominal p-value 0.724 and 0.011, respectively.

Upon request, the Applicant conducted a sensitivity analysis of the primary endpoint (Table 20).

Table 20: Positive and Negative Syndrome Scale (PANSS) - 18-Item Brief Psychiatric Rating Scale (BPRS) Score Change from Baseline. Randomized Population (include data after premature treatment discontinuation)

Visit		Ilo 4-8 mg (N=153)	Ilo 10-16 mg (N=154)	Ris (N=153)	Pbo (N=156)	Ilo 4-8 mg vs Pbo	Ilo 10-16 mg vs Pbo	Ris vs Pbo
Week 6	n	153	154	152	156			
	Adj. Change	7.27	8.64	9.87	5.65	1.63	2.99	4.22
	Adj. Change (SE)	1.42	1.36	1.35	1.41	1.69	1.65	1.66
	95% C.I.	4.48, 4.48	5.98, 5.98	7.23, 7.23	2.89, 2.89	-1.69, 4.95	-0.24, 6.22	0.96, 7.47
	p-value					0.3361	0.0696	0.0111

Notes: Results are from MMRM model with post-baseline missing data imputed using jump-to-reference imputations (1000 imputations) and summarized using Rubin's rules.

Study 3005: 6-week efficacy, dose range

Study title: A randomized, double-blind, placebo- and risperidone-controlled, multicentre 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 q.d.

Methods

This was a prospective, randomized, double-blind, placebo- and active-controlled, multicentre study to evaluate the efficacy and safety of iloperidone (12-16 mg/d or 20-24 mg/d) and risperidone (6-8 mg/d).

Study Participants

Main inclusion criteria:

- Patients were to have a diagnosis of schizophrenia according to DSM-IV criteria. This includes DSM-IV diagnoses of schizophrenia (i.e., 295) with suffixes 10 (disorganized), 30 (paranoid), 70 (schizoaffective), or 90 (undifferentiated).
- A PANSS total score of at least 60 at screening and baseline.
- A rating of at least "4" ("moderate") on at least 3 of the following 5 PANSS positive symptoms: delusions, conceptual disorganization, hallucinatory behaviour, grandiosity, and suspiciousness/persecution.

Main exclusion criteria:

- Schizophreniform disorder (295.40).
- Any other primary psychiatric diagnosis (Axis I) or comorbid diagnosis (Axis II), according to DSM-IV criteria.
- A diagnosis or history suggestive of chemical dependence according to DSM-IV criteria, or toxic psychosis in the preceding 6 months, or a clinical presentation possibly confounded by the use of recreational drugs or alcohol.

- Patients who suffered from other medical conditions which could have been expected to progress, recur, or change to such an extent that they may have put the patient at special risk or bias the assessment of the clinical and the mental status of the patient to a significant degree (e.g., second degree or higher heart block, severe or deteriorating cardiovascular disease, clinically relevant ECG abnormality, severe obstructive lung disease, untreated thyroid disease, known HIV or Hepatitis C infection, myocardial infarction within the past 6 months, insulin-dependent diabetes, etc.) were to be excluded. This included any non-psychiatric coexistent disease state that had not been maintained in a stable condition for at least 3 months prior to baseline.

Treatments

This study had three phases: pre-randomization, short-term double-blind, and a long- term open-label phase. Figure 4 summarizes the study design for the pre-randomization and initial double-blind phases.

Figure 4: Study 3005, study schema

Pre-randomization phase		Short-term double-blind phase (bid dosing)	
Day -30 to -3	Day -2 to 0[a]	Day 1 to 7	Day 8 to 42
Screening	Single blind placebo run- in period (bid dosing)	Fixed titration period (mg/d)	Flexible maintenance period (mg/d)
	Placebo	Ilo low: 2→4→8→12	Ilo low: 12[b] or 16
		Ilo high:2→4→8→12→16→20	Ilo high: 20[b] or 24
		Pbo	Pbo
		Ris: 2→4→6	Ris: 6[b] or 8

Ilo=iloperidone; Ris=risperidone; Pbo=placebo

[a] Placebo run-in period lasted a minimum of 3 days; the last day of placebo run-in period was baseline (Day 0)

[b] Titration target dose

For the iloperidone 12-16 mg/d group, the dosage was increased every other day until the target dosage of 12 mg/d was reached on Day 7. For the 20-24 mg/d group, daily dosage increases were made up to 12 mg/d (Days 4 and 5). Thereafter, the dosage was increased every day until the target dose of 20 mg/d was reached on Day 7. The target dose during titration was the lower of the dosages (Level A) in each treatment group. The investigator was given the option of increasing the dosage to a higher maintenance dose (Level B) in order to explore additional benefit. Thus, if randomized to iloperidone 12 mg/d (Level A), the dosage could be increased to 16 mg/d (Level B); if randomized to iloperidone 20 mg/d iloperidone (Level A), an increase to 24 mg/d (Level B) was allowed, and if randomized to risperidone, an increase from 6 to 8 mg/d was permitted.

Patients who consented to participate in the study agreed to be hospitalized for at least 10 days (i.e., during the placebo run-in and the titration period of the initial double-blind phase) and at any other time throughout the study, if medically necessary.

No standardised criteria for treatment rescue were defined. Rescue medication was used at the investigator's discretion. *Insomnia* was treated with chloral hydrate or zolpidem, *agitation/severe restlessness* was treated with chloral hydrate or lorazepam and *EPS* were treated with benztropine.

Objectives

The primary objective of the 6-week double-blind phase of the study was to determine the efficacy and safety of iloperidone 12-16 mg/d (administered as 6 or 8 mg bid) and 20-24 mg/d (10 or 12 mg bid) and risperidone 6-8 mg/d (3 or 4 mg bid) compared with placebo over 42 days in patients with schizophrenia or schizoaffective disorder.

The secondary objective was to demonstrate the effect of iloperidone on negative symptoms of schizophrenia over 42 days. The primary measure of this secondary efficacy variable was the change in the PANSS negative syndrome subscale from baseline at endpoint (Week 6 or premature discontinuation).

Outcomes/endpoints

The primary efficacy endpoint was the change from baseline to end of study (Day 42 or premature discontinuation) on the 18-item PANSS-derived BPRS score in the LOCF dataset. The primary treatment comparison was between the iloperidone 12-16 mg/d group and the placebo group.

The secondary treatment comparison of interest was between the iloperidone 20-24 mg/d group and the placebo group at endpoint.

Sample size

The sample size calculation was based on the adjusted mean change from baseline at endpoint on the BPRS, where the standard deviation (SD) = 12. This standard deviation was based on data from iloperidone study 3000 comparing a fixed dose of iloperidone 12 mg/d to placebo. A sample size of 150 patients per arm allowed the detection of an ~4-point difference between iloperidone and placebo with 80% power and with a two-sided alpha=0.05.

Randomising the initial 300 patients in a ratio of 2:1:1 (iloperidone 12-16 mg/d, risperidone, and placebo) gave patients a 75% chance of being randomised to active treatment. With the addition of iloperidone 20-24 mg/d arm, the randomisation ratio was changed to 1:2:1:1 (iloperidone 12-16 mg/d, iloperidone 20-24 mg/d, risperidone, and placebo) for the planned subsequent 375 patients, and increased the power of the iloperidone 12-16 mg/d group versus placebo comparison to 88% while allowing patients an 80% chance of being randomised to active medication.

Randomisation and blinding (masking)

Initially patients were randomised to one of three treatment groups in a 2:1:1 ratio (iloperidone 12-16 mg/d, risperidone, and placebo). Randomisation to iloperidone 20-24 mg/d (10 or 12 mg bid) was initiated after approximately half of the anticipated enrolment was completed because, by this time, study 3004 had shown that patients might benefit from iloperidone doses >16 mg/d. This meant that patients were subsequently randomised in a ratio of 1:2:1:1 to receive treatment with iloperidone 12-16 mg/d, iloperidone 20-24 mg/d, risperidone, or placebo to balance the treatment arms. This change in the randomisation ratio based on the results of study 3004 was pre-specified in the protocol.

Blinding was accomplished by means of a double-dummy design. During the placebo run-in period and the short-term double-blind phase, three tablets and one capsule were administered bid.

Patients qualified for admission were randomised to treatment groups by the IVRS. The IVRS was also used to maintain the blind by assigning study medication to patients throughout the study.

Single-blind study medication (placebo) used during the placebo run-in period was identical in appearance (ie, size, colour, shape) to all double-blind study medication (iloperidone, risperidone and placebo).

The tablets of iloperidone used in the study were identical in shape and colour but contained different doses and varied in size, as follows: small-sized 1 mg tablets (embossed with a "Z1") and medium-sized 2 mg and 4 mg tablets (embossed with a "Z4"). It is noted that different dose tablets might have been labelled identically but did not necessarily contain the same dose. The small and medium placebo tablets were identical in appearance to the respectively sized iloperidone tablets.

Risperidone capsules were identical in size, shape, and colour, irrespective of dose. For blinding purposes, placebo capsules were identical in appearance to the risperidone capsules.

Randomised treatment assignment data were kept strictly confidential and were accessible only to authorised persons until unblinding. During the study the investigator and the sponsor were blinded to the drug identification (i.e., iloperidone, risperidone, placebo) but were unblinded to the relative maintenance dose level (ie, assigned doses were designated as Level A or B, which were either 12 or 16 mg/d iloperidone, 20 or 24 mg/d iloperidone, 6 or 8 mg/d risperidone, or placebo) for each patient.

Statistical methods

Analysis sets and missing data

The intent-to-treat (ITT) population included all randomised patients who received at least one dose of double-blind study medication and from whom at least one efficacy measurement was obtained while on study medication. The efficacy analysis was based on the ITT population. Efficacy measurements made more than 3 days beyond the last day study medication was administered (i.e., Day 42 or premature discontinuation) were not included in the summary analyses.

The following two data handling schemes were used for each scheduled post-baseline visit for the ITT population:

- Last observation carried forward (LOCF): The goal of this imputation scheme was to create an observation for each scheduled visit for every ITT patient. If a patient had a missing evaluation for a visit, then the immediately preceding non-missing evaluation was used.
- Observed cases (OC): In this data set, no imputation was used. It included only the data observed during the study from all ITT patients.

Analysis of the primary and secondary endpoints

A two-tailed analysis of covariance (ANCOVA) model was used for the analysis of treatment main effect of continuous variables. The terms in the model included treatment, centre, baseline (as covariate), and the treatment-by-baseline term. An additional analysis was performed for the exploration of the treatment-by-centre interaction by adding this interaction term to the above ANCOVA model. If a treatment-by-centre interaction was detected, the interaction was explored in an ad-hoc manner.

The primary efficacy variable was the change from baseline to endpoint (Day 42 or premature discontinuation) on the 18-item PANSS-derived BPRS. This endpoint analysis was based on the LOCF dataset using the ANCOVA model described above. The primary treatment comparison was between the iloperidone 12-16 mg/d group and placebo at endpoint. If this test was significant at the 0.05 level, the subsequent pairwise comparison of the iloperidone 20-24 mg/d group with placebo was also tested at the 0.05 level. If the comparison of iloperidone 12-16 mg/d group with placebo was not significant, comparison of the iloperidone 20-24 mg/d group with placebo was not considered significant, regardless of the nominal significance level.

Categorical variables were analysed using the Cochran-Mantel-Haenszel (CMH) test blocking on centres.

Interim analysis

No interim analyses were planned or conducted.

Results

Participant flow

Table 21: Study 3005. Patient disposition, by treatment. All randomized patients

Treatment Group	Ilo 12-16 mg/d	Ilo 20-24 mg/d	Ris 6-8	Pbo	Total
Randomized[a]	N=244	N=145	N=157	N=160	N=706
	n (%)	n (%)	n (%)	n (%)	n (%)
Completed	127 (52)	85 (59)	111 (71)	87 (54)	410 (59)
Discontinuations	113 (46)	59 (41)	45 (29)	73 (46)	290 (41)
Primary reason for discontinuation					
Treatment emergent Adverse Event	8 (3)	7 (5)	7 (4)	4 (3)	26 (4)
Non-treatment emergent Adverse Event	1 (0)	0	1 (1)	2 (1)	4 (1)
Abnormal Laboratory Values	1 (0)	0	1 (1)	1 (1)	3 (0)
Abnormal Test Procedure	0	0	0	1 (1)	1 (0)
Unsatisfactory Therapeutic Effect	57 (23)	33 (23)	12 (8)	46 (29)	148 (21)
Condition No Longer Requires Study Drug	1 (0)	0	0	0	1 (0)
Protocol Violation	4 (2)	1 (1)	3 (2)	1 (1)	9 (1)
Withdrawal of Consent	29 (12)	12 (8)	14 (9)	12 (8)	67 (9)
Lost to Follow-up	9 (4)	6 (4)	7 (4)	6 (4)	28 (4)
Administrative Problems	3 (1)	0	0	0	3 (0)
Death	0	0	0	0	0

Ilo=iloperidone; Ris=risperidone; Pbo=placebo. [a] Nine patients were randomized but did not take double-blind study medication

Recruitment

First patient recruited: 15-Apr-2000. Last patient completed: 15-Mar-2001.

Conduct of the study

No changes were made to the protocol that might have affected the statistical integrity of the efficacy results.

Baseline data

Baseline data is presented in Table 22.

Table 22: Study 3005. Baseline data

Treatment Group	Ilo 12-16 mg/d	Ilo 20-24 mg/d	Ris 6-8	Pbo	Total
	N=244 n (%)	N=145 n (%)	N=157 n (%)	N=160 n (%)	N=706 n (%)
Age (yr)					
Mean ±SD	38.9±11.0	37.3±10.7	39.8±10.4	39.0±10.3	38.8±10.7
Median	38.0	38.0	39.0	39.5	39.0
<18	0	0	0	0	0
18-24	26 (11)	21 (14)	10 (6)	14 (9)	71 (10)
25-44	146 (60)	82 (57)	95 (61)	97 (61)	420 (59)
45-65	72 (30)	42 (29)	52 (33)	48 (30)	214 (30)
>65	0	0	0	1 (1)	1 (0)
Sex - n(%)					
Male	146 (60)	99 (68)	96 (61)	94 (59)	435 (62)
Female	98 (40)	46 (32)	61 (39)	66 (41)	271 (38)
Race n(%)					
Caucasian	163 (67)	102 (70)	120 (76)	110 (69)	495 (70)
Black	68 (28)	33 (23)	27 (17)	39 (24)	167 (24)
Oriental	2 (1)	3 (2)	2 (1)	2 (1)	9 (1)
Other	11 (5)	7 (5)	8 (5)	9 (6)	35 (5)
Weight (kg)					
N	237	144	154	159	694
Mean	82.08	81.08	82.64	83.12	82.23
SD	20.26	18.33	19.68	20.24	19.71
Median	79.50	77.95	81.30	78.00	79.00
Minimum	44.0	45.9	45.0	46.0	44.0

Treatment Group	Ilo 12-16 mg/d	Ilo 20-24 mg/d	Ris 6-8	Pbo	Total
Maximum	152.0	143.6	164.1	140.9	164.1
Height (cm) N	238	143	153	160	694
Mean± SD	170.7±9.9	172.5±9.2	172.2±11.0	171.1±8.6	171.5±9.8
Median	172.0	172.0	173.0	171.0	172.0
DSM-IV diagnosis					
295.10 schizophrenia disorganized	7 (3)	11 (8)	5 (3)	5 (3)	28 (4)
295.30 schizophrenia paranoid	162 (66)	89 (61)	106 (68)	108 (68)	465 (66)
295.70 schizoaffective disorder	56 (23)	31 (21)	31 (20)	40 (25)	158 (22)
295.90 schizophrenia undifferentiated	19 (8)	14 (10)	15 (10)	7 (4)	55 (8)

Ilo=iloperidone; Ris=risperidone; Pbo=placebo

Numbers analysed

See Table 21.

Outcomes and estimation

Primary outcome: For the primary efficacy comparison at endpoint, the iloperidone 12-16 mg/d group had a numerically greater reduction in the BPRS mean score from baseline compared to the placebo group, but the difference was not statistically significant (p=0.090). See Table 23. A nominally statistically significantly greater reduction on the BPRS was achieved at endpoint for the iloperidone 20-24 mg/d group compared to the placebo group (p=0.010).

Table 23: Study 3005. BPRS: Mean change (adjusted) from baseline score

	Ilo 12-16 mg/d	Ilo 20–24 mg/d	Ris	Pbo
Baseline	54.4	54.9	55.0	55.4
Week 1	2.6	3.2	4.9*	2.8
Week 2	4.9	5.5	8.4*	4.0
Week 3	6.9*	6.7*	9.8*	4.1
Week 4	7.5*	8.1*	10.9*	5.1
Week 5	7.7*	8.6*	11.6*	5.2
Week 6	7.1	8.6*	11.5*	5.0

Ilo=iloperidone; Ris=risperidone; Pbo=placebo. BPRS=18-item Brief Psychiatric Rating Scale score
* P<0.05 (two-tailed) compared with placebo; based on t-test using ANCOVA model.

Secondary outcomes - 20% or greater improvement in BPRS

The proportion of patients with a 20% or greater improvement over baseline for BPRS is shown in Table 24. A nominally statistically significant difference between both iloperidone groups and placebo was shown in week 3 only. For risperidone the difference compared to placebo was shown from week 2 through 6.

Table 24: Study 3005. 18-item BPRS score, percent patients with ≥20% improvement. Intent-to-treat population - Last observation carried forward

	Ilo 12-16 mg		Ilo 20-24 mg		Ris		Pbo		Ilo 12-16 mg vs Pbo	Ilo 20-24 mg vs Pbo	Ris vs Pbo
Visit	N	n(%)	N	n(%)	N	n(%)	N	n(%)	P values for Pairwise Comparisons+		
Week 1	230	67 (29)	141	32 (23)	148	49 (33)	152	42 (28)	0.782	0.353	0.244
Week 2	230	101 (44)	141	64 (45)	148	86 (58)	152	58 (38)	0.200	0.220	<0.001*
Week 3	230	110 (48)	141	67 (48)	148	90 (61)	152	54 (36)	0.025*	0.033*	<0.001*
Week 4	230	126 (55)	141	76 (54)	148	95 (64)	152	68 (45)	0.076	0.090	0.002*
Week 5	230	126 (55)	141	78 (55)	148	99 (67)	152	70 (46)	0.103	0.095	<0.001*
Week 6	230	122 (53)	141	77 (55)	148	99 (67)	152	66 (43)	0.079	0.057	<0.001*

Ilo=iloperidone; Ris=risperidone; Pbo=placebo. BPRS=18-item Brief Psychiatric Rating Scale score

Reduction on the PANSS-T score

In the LOCF dataset, the iloperidone 12-16 mg/d group showed a nominally statistically significantly greater reduction than placebo on the PANSS-T score at Weeks 3 through 5; for the iloperidone 20-24 mg/d group, this was seen at Weeks 3 through 6. In the risperidone group a nominally statistically significantly greater reduction compared to placebo was achieved from Weeks 1 through 6.

Global Improvement scale of the Clinical Global Impression (CGI-C)

In the LOCF dataset, the proportion of patients achieving improvement on the CGI-C was nominally statistically significantly greater in the iloperidone 20-24 mg/d group than in the placebo group from Weeks 3 through 6. The results for iloperidone 12-16 mg/d group were not nominally significantly different from the placebo group at any time during the study. In the risperidone group, a nominally statistically significantly greater proportion of patients showed clinical improvement compared to placebo at Weeks 1 to 6.

Ancillary analyses

The Applicant provided post-hoc analyses of treatment response defined as at least 30% and at least 40% reduction on the 18-item BPRS score and the PANSS total score compared to baseline, in schizophrenia patients only.

In the 12-16 mg iloperidone group, 25.3% of patients had at least a 30% reduction on the BPRS at week 6 compared to 16.9 % in the placebo group (nominal p 0.040). In the 20-24 mg group 22.5% were responders at week 6 (nominal p 0.079).

The risperidone treatment group separated from the placebo group at week 3, with 34.5% of patients being responders at week 6 (nominal p 0.002).

Study 3101: 4-week efficacy

Study title: A randomized, double-blind, placebo- and ziprasidone-controlled, multicentre 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

Methods

Study Participants

Main inclusion criteria:

- Diagnosis of schizophrenia according to DSM-IV criteria. This includes DSM-IV diagnoses of schizophrenia (i.e., 295) with suffixes 10 (disorganized), 30 (paranoid), or 90 (undifferentiated).
- Severity of illness:
  - CGI-S ≥ 4 at baseline.
  - PANSS-T score ≥ 70 at screening and baseline.
  - A rating of ≥"4" ("moderate") on ≥2 of the following 4 PANSS positive (PANSS-P) symptoms: delusions, conceptual disorganization, hallucinatory behaviour, and suspiciousness/persecution at screening and baseline.

Main exclusion criteria:

- Patients who met the DSM-IV criteria for schizophreniform disorder (295.40) and schizoaffective disorder (295.70).
- Patients with any other primary psychiatric diagnosis (Axis I) or any axis to interfere with compliance to the protocol.
- Patients who had a diagnosis or history suggestive of chemical dependence according to DSM-IV criteria, or toxic psychosis in the preceding 6 months, or a clinical presentation possibly confounded by the use of recreational drugs or alcohol.
- Patients who suffered from other clinically significant medical conditions, which could have been expected to progress, recur, or change to such an extent that they may have put the patient at special risk or bias the assessment of the clinical and the mental status of the patient to a significant degree (e.g., second-degree or higher heart block; a history of clinically significant valve disorders; New York Heart Association [NYHA] Class II-IV heart failure; dilated, restrictive, or hypertrophic cardiomyopathy; severe or deteriorating cardiovascular disease; clinically relevant ECG abnormality [defined as PR >240 msec, QRS complex >110

msec, QTcF >500]; […] were to be excluded. This included any nonpsychiatric coexistent disease state that had not been maintained in a stable condition for at least 3 months prior to baseline.

- Patients with known congenital long QT syndrome.

Treatments

This was a prospective, randomized, double-blind, placebo- and ziprasidone-controlled, parallel-group, multicentre study to evaluate the efficacy and safety of fixed doses of iloperidone and ziprasidone in patients with schizophrenia. It had 3 phases: the pre-randomisation phase; the short-term, double-blind phase; and the long-term, open-label phase. See Figure 5.

Figure 5: Study 3101, study schema

Pre-randomization phase		**Short-term double-blind phase (b.i.d. dosing)**	
Screening visit	Baseline visit	Titration period (mg/d)	Maintenance period (mg/d)
Days -14 to -3	Day 0	Days 1 to 7	Days 8 to 28
		iloperidone 2→4→8→12→16→20→24	iloperidone 24
		placebo	placebo
		ziprasidone 40→40→80→80→120→120→160	ziprasidone 160

All patients were to be hospitalised during the 4 weeks of the short-term, double-blind study (Days 1 to 28). Day passes could be allowed at the Investigator's discretion during Weeks 3 and 4 to patients who had a responsible caregiver who could provide a stable residence. This information was to be documented in the source documents. On Weeks 3 and 4, three day-passes were allowed for each week (maximum of 6 passes total). These passes could not be granted in consecutive days (e.g., a patient was not able to receive a weekend pass for Saturday and Sunday). Patients who were granted day passes were required to be at the hospital for dosing. Caregivers were advised to follow all of the protocol requirements. Patients could have unlimited supervised outings with study staff personnel during Weeks 2 to 4. One emergency supervised outing could be granted by the Investigator during Week 1, if needed.

Objectives

The first primary objective of the study was to determine the efficacy of iloperidone 24 mg/d as measured by the PANSS-T score as compared with placebo in the overall population.

A second primary objective was to determine the efficacy of a 24-mg/d (12 mg b.i.d.) iloperidone dose in schizophrenic patients lacking the CNTF FS63Ter polymorphism compared with schizophrenic patients treated with placebo lacking the CNTF FS63Ter polymorphism.

There were two secondary objectives:

- to assess the efficacy of a 24-mg/d (12 mg b.i.d.) iloperidone dose in schizophrenic patients lacking the CNTF FS63Ter polymorphism versus iloperidone patients who harbour the CNTF FS63Ter polymorphism.

- to characterize the efficacy, tolerability and safety of a 24-mg/d iloperidone dose and a 160-mg/d ziprasidone dose compared with placebo, administered b.i.d. over 28 days to schizophrenic patients

Outcomes/endpoints

The primary endpoint was the change from baseline to the last scheduled observation in the PANSS-T score using the data from the short-term, double-blind phase.

The secondary endpoints were:

• Change from baseline at each time point in the 18-item BPRS extracted from the PANSS-T score

• Change from baseline at each time point for the 3 PANSS subscale scores

• The CGI-C at each time point based on the dichotomized CGI-C value to indicate improvement (minimally, much, or very much improved or worsening)

• The CGI-S at each time point

• Change from baseline in CDSS at each time point.

Sample size

The sample size calculation was based on the PANSS-derived BPRS change from baseline at endpoint where the standard deviation = 11.9 for iloperidone, 12.6 for placebo, and 12.0 for ziprasidone. The standard deviations for iloperidone and placebo were based on data from study 3005, comparing a dose range of iloperidone 20-24 mg/d to placebo. The standard deviation for ziprasidone was based on data found in the literature.

Based on a t-test, to detect a 4-point change in BPRS between iloperidone-treated patients versus placebo, a sample size of 300 iloperidone-treated patients and 150 placebo-treated patients was needed in order to have 90% power with a two-sided alpha=0.05.

Using this sample size and assuming that 210 iloperidone-CNTF FS63Ter(-) and 90 iloperidone-CNTF FS63Ter(+) patients would be enrolled provided 60% power with a two-sided alpha=0.05 to detect a 4-point change in BPRS between iloperidone-treated patients with the CNTF FS63Ter(-) genotype versus all iloperidone-treated patients with the CNTF FS63Ter(+) genotype.

A sample size of 150 ziprasidone-treated patients would provide 80% power with a 2-sided alpha=0.05 to detect a 4-point change in BPRS between ziprasidone-treated patients versus placebo-treated patients.

Randomisation and blinding (masking)

Patients were randomised in a 2:1:1 ratio to receive treatment with iloperidone, ziprasidone, or placebo. Randomisation was performed using IVRS. Randomisation was centralized by country and utilised randomization blocks consisting of 4 iloperidone treatment groups, 2 ziprasidone treatment groups, and 2 placebo treatment groups.

This study was double-blind. The sponsor, the Investigator and his/her staff, and the subject were unaware of whether the subject received an active or placebo treatment during the short-term, double-blind phase of the study. In order to maintain the blind, all study drug used in the short-term, double-

blind phase was provided as an over-encapsulated tablet or capsule to ensure that they were identical in appearance (i.e., same size, colour, and shape).

There were no instances of the blind being broken during this study.

Statistical methods

Analysis sets

All efficacy analyses were conducted in the modified ITT population, the primary study population. The modified ITT population contained all randomized patients who received at least one dose of double-blind study medication and from whom a baseline PANSS score measurement was obtained and at least one post-baseline PANSS efficacy measurement was obtained while on study medication. If a measurement was made more than 3 days after the last study medication administration, then the evaluation was not considered as an endpoint and was excluded from the analyses.

If a patient was randomized in error at a second site after being randomized once, the data from the second site were not included in the modified ITT population for efficacy.

Analysis of the primary endpoint

The primary efficacy endpoint (PANSS-T) was to be analysed using a mixed-model repeated measures (MMRM) model. The covariates were treatment group, adjusted baseline response (patient's baseline minus the average baseline for all patients), and centre. No constant (intercept) term was included. In SAS PROC MIXED, the covariance structure was implemented by the REPEATED statement with the option TYPE=UN for "unstructured." If unscheduled or early termination assessments occurred subsequent to scheduled assessment, then this value was carried forward to the missing next scheduled visit (but did not carry beyond that next scheduled visit to the end of the study).

Tests of efficacy were computed under two additional procedures as sensitivity analyses of assumptions about missing values: a last observation carried forward (LOCF) analysis and an observed-cases (OC) analysis. Both procedures used analysis of covariance (ANCOVA) models.

If the efficacy results from these sensitivity analyses were not consistent with those from the MMRM, then additional sensitivity analyses were to be conducted under a set of pattern-mixture models (PMMs) that assume patients' missing post-dropout responses were missing not at random (MNAR).

A Cochran-Mantel-Haenszel test was used to compare number of patients who improved by at least a 20% in each group.

Analysis of the secondary endpoints

Analyses of continuous secondary endpoints were conducted similarly to the primary efficacy variable.

Multiplicity

If the primary endpoint was significant at alpha=0.05 in the overall population, a step-down primary objective was tested. Initially, the step-down primary objective was to determine the efficacy of iloperidone 24 mg/d in patients with the CNTF FS63Ter(-) genotype compared to all patients treated with placebo as measured by the PANSS total rating. However, in protocol amendment 4 (dated 4-Aug-2006, 570 patients enrolled), the step-down primary objective was changed to determining the efficacy of iloperidone 24 mg/d in patients with the CNTF FS63Ter(-) genotype compared to placebo-treated patients with the CNTF FS63Ter(-) genotype as measured by the PANSS-T score.

Interim analysis

No interim analyses were planned or performed.

Results

Participant flow

Table 25: Study 3101. Patient disposition, by treatment (all randomized patients)

	Iloperidone 24 mg/d	Ziprasidone 160 mg/d	Placebo	Total
	n (%)	n (%)	n (%)	n (%)
Randomization assigned	303 (100)	151 (100)	152 (100)	606 (100)
Randomization assigned in error	8	2	3	13
Randomization at second site post initial randomization[a]	6	2	2	10
Randomization of screening failure[b]	2	0	1	3
Patients randomized[c]	295 (97.4)	149 (98.7)	149 (98.0)	593 (97.9)
Completed short-term, double-blind phase[d]	193 (65.4)	98 (65.8)	90 (60.4)	381 (64.2)
Discontinued during short-term, double-blind phase[d]	102 (34.6)	51 (34.2)	59 (39.6)	212 (35.8)
Primary reason for discontinuation from short-term, double-blind phase[e]				
Protocol deviation	2 (2.0)	1 (2.0)	1 (1.7)	4 (1.9)
Adverse event(s)[f]	16 (15.7)	13 (25.5)	11 (18.6)	40 (18.9)
Lost to follow-up	0	0	2 (3.4)	2 (0.9)
Death	0	0	0	0
Patient withdrew consent	59 (57.8)	23 (45.1)	21 (35.6)	103 (48.6)
Unsatisfactory therapeutic effect	21 (20.6)	12 (23.5)	19 (32.2)	52 (24.5)
Other	4 (3.9)	2 (3.9)	5 (8.5)	11 (5.2)

Recruitment

First patient enrolled: 18-Nov-2005. Last patient completed: 26-Sept-2006.

Conduct of the study

No changes were made to the protocol that might have affected the statistical integrity of the efficacy results.

Baseline data

Baseline data is presented in Table 26.

Table 26: Study 3101. Demographic and baseline clinical characteristics by treatment (all randomized patients)

Characteristic	Iloperidone 24 mg/d (N=295)	Ziprasidone 160 mg/d (N=149)	Placebo (N=149)	Total (N=593)
Age, yr				
N	295	149	149	593
Mean (SD)	39.5 (10.4)	40.0 (9.9)	40.7 (10.4)	39.9 (10.3)
Median	41.0	41.0	41.0	41.0
Range	18 to 65	20 to 61	19 to 64	18 to 65
Age, yr (n [%])				
<18	0	0	0	0
18-24	26 (8.8)	9 (6.0)	8 (5.4)	43 (7.3)
25-44	171 (58.0)	86 (57.7)	85 (57.0)	342 (57.7)
45-65	98 (33.2)	54 (36.2)	56 (37.6)	208 (35.1)
>65	0	0	0	0
Sex, n (%)				
Male	245 (83.1)	113 (75.8)	114 (76.5)	472 (79.6)
Female	50 (16.9)	36 (24.2)	35 (23.5)	121 (20.4)
Race, n (%)				
American Indian or Alaska Native	2 (0.7)	0	1 (0.7)	3 (0.5)
Asian	25 (8.5)	12 (8.1)	15 (10.1)	52 (8.8)
Black or African American	147 (49.8)	76 (51.0)	76 (51.0)	299 (50.4)
Native Hawaiian or Other Pacific Islander	2 (0.7)	0	0	2 (0.3)
White	111 (37.6)	51 (34.2)	46 (30.9)	208 (35.1)

Characteristic	Iloperidone 24 mg/d (N=295)	Ziprasidone 160 mg/d (N=149)	Placebo (N=149)	Total (N=593)
Other	8 (2.7)	10 (6.7)	11 (7.4)	29 (4.9)
Weight, kg				
N	295	149	149	593
Mean (SD)	82.18 (17.40)	80.46 (17.10)	81.09 (18.68)	81.47 (17.64)
Median	80.90	79.55	81.73	80.90
Range	46.0 to 145.7	38.0 to 125.5	42.0 to 127.3	38.0 to 145.7
Height, cm				
N	295	148*	149	592
Mean (SD)	173.76 (9.22)	172.70 (10.05)	172.00 (10.47)	173.05 (9.77)
Median	175.00	173.00	172.72	173.99
Range	144.8 to 200.7	144.0 to 193.0	145.0 to 195.6	144.0 to 200.7
DSM-IV diagnosis, n (%)				
295.10 Schizophrenia disorganized	13 (4.4)	3 (2.0)	7 (4.7)	23 (3.9)
295.30 Schizophrenia paranoid	246 (83.4)	127 (85.2)	128 (85.9)	501 (84.5)
295.90 Schizophrenia undifferentiated	36 (12.2)	19 (12.8)	14 (9.4)	69 (11.6)

Mean baseline values for efficacy parameters (PANSS-T, PANSS-P, PANSS-N, PANSS-GP, BPRS, CGI-S, and CDSS) were similar among the 3 treatment groups, with the exception of the PANSS-P score, which was significantly higher in the iloperidone group compared with the placebo group; mean (SD) 24.91 (3.83) and 23.52 (3.71) respectively (p=0.001).

Numbers analysed

See Table 25.

Outcomes and estimation

Primary outcome: The primary analysis was the comparison of iloperidone to placebo using the MMRM model with baseline as covariate. Based on this analysis, a statistically significantly greater improvement from baseline in PANSS-T score was demonstrated in the iloperidone group compared with placebo at Day 28 (–12.01 at Day 28, P < 0.01). Patients who received iloperidone experienced an average -4.92 points more improvement than patients who received placebo. See Table 27.

Table 27: Study 3101: PANSS-T: Adjusted mean change (standard error) from baseline to Day 28 (MMRM analysis, modified ITT population)

	Iloperidone 24 mg/d (N=283)	Ziprasidone 160 mg/d (N=144)	Placebo (N=140)
Baseline	92.88	90.95	90.48
Day 7	–4.29 (0.62)	–6.56 (0.87)	–4.22 (0.89)
Day 10	–7.01 (0.72)	–8.60 (1.01)[a]	–5.16 (1.03)
Day 14	–8.65 (0.86)	–10.02 (1.20)[a]	–5.85 (1.23)
Day 21	–10.56 (0.93)[a,b]	–11.54 (1.31)[a]	–6.84 (1.34)
Day 28	–12.01 (1.03)[c,d]	–12.27 (1.44)[a]	–7.08 (1.48)

MMRM = mixed-model repeated measures; ITT = intent-to-treat; PANSS-T = Positive and Negative Syndrome Scale total score.
[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).

Patients in the iloperidone group lacking the CNTF FS63Ter polymorphism (CNTF (-)) exhibited significantly greater improvement from baseline in PANSS-T score than did patients in the placebo group who also lacked the polymorphism.

Secondary outcome:

At day 28, 45.2%, 45.8%, and 37.1% of iloperidone-, ziprasidone-, and placebo-treated patients, respectively, showed a ≥20% improvement in PANSS-T score from baseline in the LOCF dataset. The comparisons to placebo were not nominally significant.

A nominally statistically significantly greater reduction (improvement) from baseline in BPRS score was demonstrated by the iloperidone group compared with placebo at study endpoint (–7.39 and –4.62 at Day 28, respectively, P = 0.013). The ziprasidone group also exhibited a nominally statistically significantly greater reduction from baseline in BPRS score compared with placebo at Day 21 (-6.97 and -4.46, respectively, P = 0.032) and at study endpoint (–7.21 and –4.62 at Day 28, respectively, P = 0.042).

A numerically greater percentage of patients receiving iloperidone or ziprasidone exhibited a ≥20% reduction (improvement) from baseline to Day 28 of treatment in BPRS scores compared with placebo, but the comparisons to placebo were not significant. At Day 28, 137/283 (48.4%), 68/144 (47.2%), and 58/140 (41.4%) of iloperidone-, ziprasidone, and placebo-treated patients, respectively, showed a ≥20% improvement from baseline. Patients in the iloperidone group lacking the CNTF polymorphism exhibited significantly greater improvement from baseline in BPRS score than did patients in the placebo group who also lacked the polymorphism.

In the LOCF dataset, the proportions of patients who were improved (defined as minimally, much, or very much improved) on the CGI-C at day 28 was 64.7% in the Ilo 24 mg/d group compared to 52.1% in the placebo group, nominal p-value <0.05, and nominally significant difference was shown at day 21 (62.9% vs 49.3%). In the ziprasidone group, a nominally significant difference compared to placebo was shown at day 14 and 21, but not at day 28.

Ancillary analyses

The Applicant provided post-hoc analyses of treatment response defined as at least 30% and at least 40% reduction on the PANSS total score compared to baseline. In the iloperidone group, 15.9% of patients had at least a 30% reduction on the PANSS-T at day 28 compared to 12.1 % in the placebo group (nominal p 0.404). In the ziprasidone group this proportion was 18.1% (nominal p 0.158). With treatment response defined as at least 40% reduction, the proportion of responders at day 28 were 4.2%, 6.3% and 5.0% in the iloperidone, ziprasidone and placebo groups respectively with no nominally statistically significant differences between the groups at any time during the study.

Upon request, the Applicant conducted a sensitivity analysis of the primary endpoint (Table 28).

Table 28: Positive and Negative Syndrome Scale (PANSS) - Total Score Change from Baseline Short-Term Double-Blind Phase (Day 1-28). Randomized Population (include data after premature treatment discontinuation)

Visit		Ilo (N=295)	Zip (N=149)	Pbo (N=149)	Ilo vs Pbo	Zip vs Pbo	Ilo vs Zip
Day 28 (Week 4)	n	295	149	149			
	Adj. Change	-11.15	-11.53	-8.10	-3.05	-3.43	0.39
	Adj. Change (SE)	1.16	1.56	1.53	1.82	2.10	1.80
	95% C.I.	-13.41, -13.41	-14.60, -14.60	-11.10, -11.10	-6.61, 0.52	-7.54, 0.68	-3.14, 3.92
	p-value				0.0937	0.1015	0.8297

Notes: Results are from MMRM model with post-baseline missing data imputed using jump-to-reference imputations (1000 imputations) and summarized using Rubin's rules.

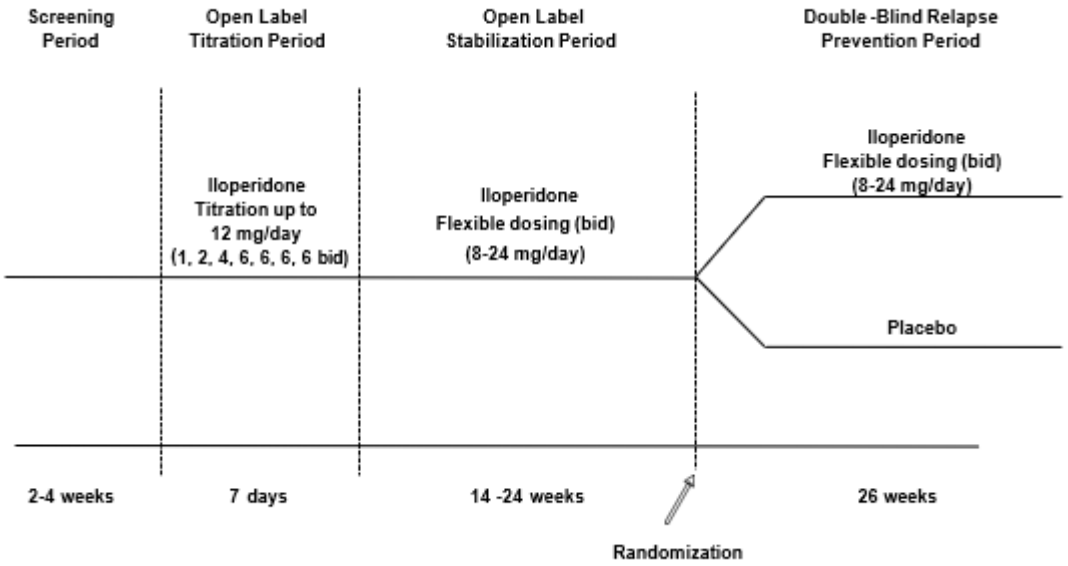
Study 2301: relapse prevention

Study title: A multicentre, 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

Methods

This was a multicentre, randomised, double-blind, placebo-controlled, parallel-group study with 2 treatment parts: Part A, relapse prevention, and Part B, an optional long-term open-label extension. An overview of Part A is presented in Figure 6.

Figure 6: Study schema 2301, part A



Study Participants

Main inclusion criteria

- A diagnosis of schizophrenia according to DSM-IV criteria for at least 1 year. This includes DSM-IV diagnoses of schizophrenia (i.e., 295) with suffixes 10 (disorganized), 20 (catatonic), 30 (paranoid), 60 (residual), or 90 (undifferentiated).
- Patients will be in need of ongoing psychiatric treatment and must have a documented reason why a change in treatment is warranted which might reasonably be expected to possibly lead to a clinical improvement. This will be recorded as either:
    - Insufficient efficacy (i.e., not fully in remission or experiencing residual symptoms) and / or
    - Tolerability/safety concerns (e.g. weight gain, extrapyramidal symptoms, etc)
- At the screening visit patients will have a PANSS of no more than 100 and a CGI-S of no more than 5 (i.e. must not be severely ill or worse).

Main exclusion criteria

- Patients who meet the DSM-IV criteria for schizophreniform disorder (295.40) and schizoaffective (295.70) will be excluded.
- Patients with active symptoms of any other primary psychiatric diagnosis (Axis I) or prominent Axis II disorder which would interfere with compliance to the protocol.
- Patients who have a diagnosis or history suggestive of chemical dependence according to DSM-IV criteria, or drug-induced toxic psychosis in the preceding 6 months
- Patients with known clinically significant ECG abnormalities
- Patients receiving drugs that are known to prolong QTc

Randomisation inclusion criteria:

- Clinically stable throughout the last 12 weeks of the stabilization period. Clinically stable is defined as:

- Established dose of current medication that is unchanged due to efficacy in the 4 weeks prior to randomization. Dose reductions due to tolerability do not represent clinical instability.
- CGI-S score of ≤ 4.
- PANSS total score ≤ 70.
- A score ≤ 4 on each of the following individual PANSS items: P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behaviour), P6 (suspiciousness/ persecution), P7 (hostility) or G8 (uncooperativeness).
- No hospitalization or increase in level of care (partial hospitalization) to treat exacerbation

Randomisation exclusion criteria:

- Patients who have been hospitalized due to suicidal ideation or suicidal behaviour; or patients considered to have serious suicidal ideation or suicidal behaviour. Patients having active suicidal ideation or behaviour at any time during the stabilization period as determined by the C-SSRS.

Treatments

Part A consisted of a screening period, open-label titration period, open-label stabilization period, and a double-blind relapse prevention period. Patients discontinued current antipsychotic treatment prior to, or within 4 days after first day of open-label titration period. During the screening period, patients who met all entry criteria for enrolment into the study entered the 7-day titration period where open-label iloperidone was titrated up to 12 mg/day total daily dose given as a bid regimen. This period was followed by a 14–24-week stabilization period where patients were allowed flexible doses (bid) of iloperidone (8, 12, 16, 20, 24 mg/day) to achieve the optimal effects for a given patient.

Patients meeting the criteria for randomization, including clinical stabilization for a minimum of 12 weeks, were eligible to proceed to the double-blind relapse prevention period. The dose of study medication could not be increased for efficacy reasons in the 4 weeks prior to entering the double-blind relapse prevention period. During the double-blind relapse prevention period, stabilized patients were randomised 1:1 to either iloperidone or placebo given as flexible dose (8, 12, 16, 20, or 24 mg per day). Patients remained in this period for 26 weeks or until relapse or impending relapse, or until withdrawal from the study.

No standardised criteria for treatment rescue were defined. Rescue medication was used at the investigator's discretion.

No standardised criteria for treatment rescue were defined. Rescue medication was used at the investigator's discretion. *Insomnia* was treated with zolpidem, *agitation/severe restlessness/insomnia* was treated with lorazepam and *EPS* were treated with benztropine.

Objectives

The primary objective was to determine the efficacy of flexible dosing of iloperidone (8, 12, 16, 20, or 24 mg/day given bid) compared with placebo in preventing relapse or impending relapse in long-term use (up to 26 weeks) in patients with schizophrenia.

The secondary objectives of this study were:

- to explore the long-term safety and tolerability of flexible dosing of iloperidone (8, 12, 16, 20, or 24 mg/day given bid);
- to explore the long-term efficacy of flexible dosing of iloperidone (8, 12, 16, 20, or 24 mg/day given bid) as measured by Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression of Severity (CGI-S), and Clinical Global Impression of Improvement (CGI-I) scores; and
- to explore the long-term safety and tolerability of flexible dosing of iloperidone (8-24 mg/day) over an additional optional 52 weeks of treatment (optional open-label extension).

Outcomes/endpoints

The primary efficacy endpoint was time to relapse or impending relapse.

Relapse or impending relapse was defined as any of the following:

- Hospitalisation (voluntary or involuntary) due to worsening of schizophrenia (not including admissions for strictly social reasons);
- An increase (worsening) of the PANSS total score of at least 30% in PANSS total score from randomization if confirmed in a second visit conducted at least 24 hours later, but within 7 days;
- Patient had suicidal, homicidal, or aggressive behaviour that was clinically significant in the Investigator's judgment.
- A CGI-I score of 6 (much worse) or 7 (very much worse) after randomisation;
- Any patient who the Investigator considered to be in need of additional treatment (ie, an increase in dose of study drug or additional antipsychotic treatment) or an increase in the level of psychiatric care for exacerbation of schizophrenia symptoms.

Sample size

The sample size calculation was based on the primary endpoint of time to relapse. Based on a 2-sided log rank test at the 0.048 level of significance and a true hazard ratio of 1.8, 123 observed events were required to achieve 0.90 power for detecting a treatment group difference. Hence, an initial sample size of 132 patients per treatment group was felt to be sufficient based upon the length of the study, the patient recruitment rate, and the patient retention rate in the Titration and Stabilization phases of the study. The significance level of 0.048 is lower than the usual 0.05 level due to the single interim analysis for efficacy and the required alpha spend based upon the O'Brien-Fleming boundary.

Randomisation and blinding (masking)

Patients were randomized 1:1 to either iloperidone or placebo given as flexible dose (8, 12, 16, 20, or 24 mg per day) using an interactive voice response system.

Patients, investigator staff, persons performing the assessments, and data analysts remained blinded to the identity of the treatment from the time of randomization until database lock, using the following methods:

- Randomisation data were kept strictly confidential until the time of unblinding and were not accessible by anyone else involved in the study with the following exceptions: in the case of medical emergencies, for the purpose of assaying plasma concentrations, and for the iDMC for the planned interim analysis.

- The identity of the treatments was concealed by the use of study drugs that were all identical in packaging, labelling, schedule of administration, appearance, taste, and odour. Over-encapsulated tablets were used to ensure identical appearance (ie, same size, colour, and shape).

Statistical methods

Analysis sets

The efficacy analyses were based on the full analysis set (FAS), defined as all randomized patients who received at least 1 dose of study drug and had at least 1 efficacy measurement while on study drug. In case of a treatment error, patients were analysed according to the treatment they were randomized to.

Analysis of the primary endpoint

The primary efficacy endpoint, time to relapse or impending relapse, was defined as the time from the first dose of double-blind study drug to the assessment at which the first relapse or impending relapse was identified. For relapses attributed solely to confirmed worsening PANSS scores, the date of the relapse was the date of the first PANSS evaluation when a $\geq$ 30% increase in total score from randomisation was observed.

Patients who discontinued the double-blind relapse prevention phase of the study early without experiencing the event were censored at the time they discontinued, while patients who completed this phase without experiencing the event were censored at their respective last visit including the end of study/early termination visit.

The primary efficacy analysis was the log rank test. A Cox regression model was also used to provide an estimated hazard ratio and corresponding nominal 95% confidence interval. In addition, plots of the Kaplan-Meier product limit estimates were used to summarize the survival distributions of the 2 groups.

For the primary efficacy analysis, the results from the interim analysis were considered the primary results.

Analysis of the secondary endpoints

For PANSS, CGI-I and SDS, change from baseline to each post-baseline time point was analysed using an analysis of covariance (ANCOVA) model with treatment and site as main effects, and the baseline score (last non-missing assessment prior to the double-blind relapse prevention phase) as a covariate. The treatment-by-site interaction and treatment-by-baseline interaction were tested and analysed only in an ad hoc exploratory fashion.

Changes from baseline were not calculated for CGI-S because this assessment was collected only once during the double-blind relapse prevention phase. Therefore, CGI-S was analysed using an analysis of variance (ANOVA) model with treatment and site as main effects.

CGI-I and CGI-S were also analysed using the full categorical structure of the variables. Treatment groups were compared at each visit using a row mean score Cochran-Mantel-Haenszel (CMH) test, controlling for site.

Missing data were handled using both last-observation-carried-forward (LOCF) and observed cases (OCs). LOCF was not conducted on CGI-S scores because there was not an observation that could be carried forward during the double-blind relapse prevention phase.

Multiplicity

The statistical inferences for secondary endpoints were not adjusted for multiplicity.

Interim analysis

This was a group sequential study which allowed for an unblinded interim analysis to be conducted in order to allow the study to stop early for efficacy. To protect the integrity of the study, the iDMC conducted the interim analysis in accordance with the iDMC charter.

The interim analysis was to occur after 60 events had been observed out of a required 123 events for the primary endpoint. The stopping boundary was a p-value less than or equal to 0.001. Although the protocol referred to this as an O'Brien-Fleming stopping boundary, it was slightly more conservative than an O'Brien-Fleming stopping boundary.

For the primary efficacy analysis, results from the interim analysis were considered as the primary results, and results from the final analysis are presented as supportive. Conclusions on the secondary endpoints and safety data were derived from the final analyses.

An unblinded sample size re-estimation approach was also planned at the interim analysis to allow the sample size to increase beyond the initial sample size. However, this sample size re-estimation was not implemented.

Results

Participant flow

Table 29. Study 2301, Patient disposition - Titration and Stabilization and Double-Blind Relapse Prevention phases - enrolled/randomized patients

	Titration and stabilisation phase Total n(%)	Ilo n(%)	Pbo n(%)	Total n(%)
Number of Patients Screened	1044			
Number of Patients Enrolled (Entering Phase) or Randomized [1]	635 (60.8)	153 (24.1)	150 (23.6)	303 (47.7)
Number of Patients who Completed Phase [2]	309 (48.7)	76 (49.7)	102 (68.0)	178 (58.7)
Primary Reason for Discontinuation [3]				
Adverse Event(s)	92(28.2)	5(6.5)	0	5(4.0)
Abnormal Laboratory Value(s)	25(7.7)	4(5.2)	2(4.2)	6(4.8)
Abnormal Test Procedure Result(s)	6(1.8)	1(1.3)	0	1(0.8)
Unsatisfactory Therapeutic Effect	28(8.6)	0	2(4.2)	2(1.6)

	Titration and stabilisation phase Total n(%)	Ilo n(%)	Pbo n(%)	Total n(%)
Subject's Condition no Longer Requires Study Drug	0	0	0	0
Subject Withdrew Consent	107(32.8)	14(18.2)	10(20.8)	24(19.2)
Lost to Follow-up	24(7.4)	6(7.8)	4(8.3)	10(8.0)
Administrative Problems	30(9.2)	45(58.4)	29(60.4)	74(59.2)
Patients who Rolled Over into Part B(OLE)	15(4.6)	41(53.2)	27(56.3)	68(54.4)
Death	1(0.3)	1(1.3)	0	1(0.8)
Protocol Deviation	13(4.0)	1(1.3)	1(2.1)	2(1.6)

DBRP = Double-Blind Relapse Prevention; ilo = iloperidone; OLE = open-label extension; pbo = placebo
[1] Percentage based on the total number of patients from previous phase, ie, patients screened (Titration and Stabilization phases) or patients enrolled (DBRP phase).
[2] Percentage based on the total number of patients enrolled (Titration and Stabilization phases) or randomized (DBRP phase).
[3] Percentage based on the total number of patients who discontinued during the phase. Notes:
1. Investigator determined the primary reason for discontinuation. Only 1 (primary) reason was recorded on Case Report Form.
2. Part A of the study (Titration and Stabilization and DBRP phases) was terminated following interim analysis. Ongoing patients in Part A were discontinued and rolled over into Part B (OLE). Reason for premature discontinuation was set to "Administrative problems."

Recruitment

First patient first visit: 07-Feb-2011. Interim analysis and data cut-off date: 17-Oct-2013
Early termination date: 13-Feb-2014. Last patient last visit: 21-Mar-2014.

Conduct of the study

No major protocol amendments were made that may have affected the robustness of the efficacy results.

Baseline data

Baseline data is presented in Figure 7 and Figure 8.

Figure 7: Study 2301. Demographic summary by treatment group - Titration and Stabilization and Double-Blind Relapse Prevention phases - enrolled/randomized patients

Parameter Statistic	Titration and Stabilization Phase Total N=635	Double-Blind Relapse Prevention Phase Ilo N=153	Pbo N=150	Total N=303
Age (years)				
N	635	153	150	303
Mean (SD)	39.6 (11.35)	38.4 (11.32)	38.2 (11.11)	38.3 (11.20)
Median	40.0	37.0	38.5	37.0
Minimum	18	18	18	18
Maximum	65	64	64	64
Age (years) n (%)				
18 – 24	70 (11.0)	20 (13.1)	19 (12.7)	39 (12.9)
25 – 44	325 (51.2)	80 (52.3)	81 (54.0)	161 (53.1)
45 – 65	240 (37.8)	53 (34.6)	50 (33.3)	103 (34.0)
Sex n(%)				
Male	400 (63.0)	96 (62.7)	82 (54.7)	178 (58.7)
Female	235 (37.0)	57 (37.3)	68 (45.3)	125 (41.3)
Female Childbearing Potential n (%)				
Able to Bear Children	160 (68.1)	42 (73.7)	53 (77.9)	95 (76.0)
Premenarche	0	0	0	0
Post Menopausal	42 (17.9)	9 (15.8)	12 (17.6)	21 (16.8)
Sterile - of Childbearing age	33 (14.0)	6 (10.5)	3 (4.4)	9 (7.2)
Height (cm)				
N	635	153	150	303
Mean (SD)	169.23 (9.950)	168.22 (9.686)	167.28 (10.715)	167.76 (10.202)
Median	170.00	169.00	166.00	168.00
Minimum	131.5	134.0	134.0	134.0
Maximum	201.0	190.0	188.0	190.0
Weight (kg)				
N	635	153	150	303
Mean (SD)	77.65 (19.534)	76.12 (19.589)	73.10 (19.713)	74.62 (19.676)
Median	75.70	75.00	70.20	72.40
Minimum	37.7	41.2	37.7	37.7
Maximum	139.0	131.0	120.1	131.0
BMI (kg/m^2)				
N	635	153	150	303
Mean (SD)	26.808 (5.6019)	26.535 (5.4894)	25.613 (5.5037)	26.079 (5.5068)
Median	25.860	25.710	24.360	25.150
Minimum	17.29	17.75	17.29	17.29
Maximum	39.91	39.91	39.84	39.91
Predominant Race n(%)				
Caucasian	280 (44.1)	74 (48.4)	77 (51.3)	151 (49.8)
Black	201 (31.7)	31 (20.3)	28 (18.7)	59 (19.5)
Asian	123 (19.4)	38 (24.8)	40 (26.7)	78 (25.7)
Native American	0	0	0	0
Pacific Islander	2(0.3)	1(0.7)	0	1(0.3)
Other	29(4.6)	9(5.9)	5(3.3)	14(4.6)
Ethnicity n (%)				
Hispanic/Latino	26(4.1)	4(2.6)	4(2.7)	8(2.6)
Chinese	1(0.2)	0	0	0
Indian (Indian Subcontinent)	117(18.4)	37(24.2)	39(26.0)	76(25.1)
Japanese	0	0	0	0
Mixed Ethnicity	19(3.0)	3(2.0)	4(2.7)	7(2.3)
Other	472(74.3)	109(71.2)	103(68.7)	212(70.0)

Figure 8. Study 2301. Schizophrenia history screening - Titration and Stabilization and Double-Blind Relapse Prevention phases - interim analysis - enrolled/randomized patients

	Titration and Stabilization Phase	Double-Blind Relapse Prevention Phase		
	Total N=587	Ilo N=99	Pbo N=96	Total N=195
DSM-IV Classification n (%)				
Disorganized	8(1.4)	1(1.0)	1(1.0)	2(1.0)
Catatonic	3(0.5)	1(1.0)	0	1(0.5)
Paranoid	556(94.7)	94(94.9)	93(96.9)	187(95.9)
Residual	2(0.3)	1(1.0)	0	1(0.5)
Undifferentiated	18(3.1)	2(2.0)	2(2.1)	4(2.1)
Age First Diagnosed (years)				
N	587	99	96	195
Mean (SD)	26.0(8.66)	25.0(8.57)	27.1(9.50)	26.0(9.07)
Median	25.0	22.0	25.0	24.0
Minimum	5	5	10	5
Maximum	57	50	57	57
Hospitalizations n (%)				
Yes	463(78.9)	86(86.9)	87(90.6)	173(88.7)
No	122(20.8)	13(13.1)	8(8.3)	21(10.8)
Unknown	2(0.3)	0	1(1.0)	1(0.5)
Number of Hospitalizations (Lifetime) n(%) [1]				
1-5	286(61.8)	50(58.1)	54(62.1)	104(60.1)
6-10	102(22.0)	21(24.4)	20(23.0)	41(23.7)
11-15	38(8.2)	10(11.6)	9(10.3)	19(11.0)
≥16	37(8.0)	5(5.8)	4(4.6)	9(5.2)

DBRP = Double-Blind Relapse Prevention; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; ilo = iloperidone; pbo = placebo
Source: Table 14.1-6.1.1
[1] Percentages are based on the total number of patients with hospitalizations in each column.
Notes:
1. Percentages are based on the total number of patients enrolled (Titration and Stabilization phases) or randomized (DBRP phase) with available data.
2. Based on patients included in interim analysis and data cut-off date 17-Oct-2013.

The mean (SD) PANSS total score at baseline of the Double-Blind Relapse Prevention phase was 55.5 (10.76) and 55.1 (10.11) in the iloperidone and placebo groups (full analysis set).

Numbers analysed

See Table 29.

Outcomes and estimation

Results for the primary endpoint, time to relapse, are presented in Table 30 and Figure 9 (interim analysis) and Table 31 and Figure 10 (final analysis).

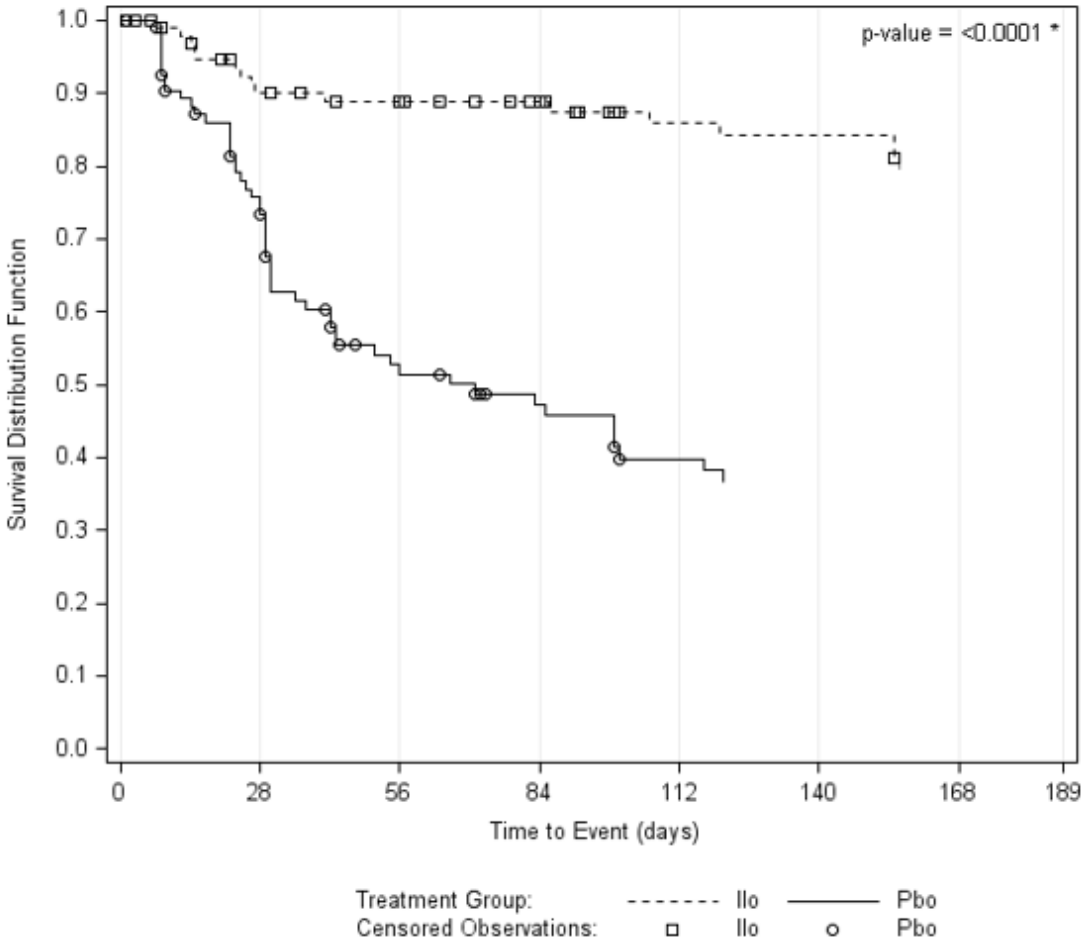
Table 30: Study 2301. Time to relapse or impending relapse (days), summary by time interval - Double-Blind Relapse Prevention phase - interim analysis – FAS

	Iloperidone N=97						Placebo N=96					
	Subjects at risk [2]		Subjects with event [3]			KM % est. without event [5]	Subjects at risk [2]		Subjects with event [3]			KM % est. without event [5]
Time interval [1] (days)	Start	End	N	%	n [4]	% (95% CI)	Start	End	N	%	n [4]	% (95% CI)
[1, 56]	97	73	10	10.3	10	88.9 (80.3, 93.9)	96	39	42	43.8	42	51.4 (40.3, 61.4)
[57, 112]	73	55	2	2.7	12	85.9 (76.4, 91.8)	39	25	8	20.5	50	39.8 (28.9, 50.4)
[113, 154]	55	54	1	1.8	13	84.3 (74.4, 90.7)	25	18	2	8.0	52	36.6 (25.9, 47.3)
[155, 182]	54	37	3	5.6	16	79.6 (68.6, 87.1)	18	11	0	0.0	52	36.6 (25.9, 47.3)
Mean time to relapse						T=139 Days						T=71 Days
Relapse Rate (95% CI) [6]						20.4 (12.9, 31.4)						63.4 (52.7, 74.1)
p-value [7]						<0.0001 *						
Hazard Ratio (95% CI) [8]						4.7 (2.7, 8.3)						

DBRP = Double-Blind Relapse Prevention; est. = estimate; FAS = Full Analysis set; ilo = iloperidone; KM = Kaplan-Meier; pbo = placebo
[1] Day 1 = date of randomization.
[2] Start: immediately prior to the start time of the interval; End: immediately prior to the end time of the interval.
[3] Within the time-interval, denominator for rate is number of patients at risk immediately prior to the start time of the interval.
[4] n = Number of patients with event up to and including the end time of the interval.
[5] KM % estimates relate to the end time of the interval. KM estimates are displayed; Greenwood formula is used for CIs of KM estimates; CIs are point-wise intervals.
[6] Relapse Rate and 95% CI relate to the end time of the [155, 182] interval. Relapse rate estimates are calculated as: 100% - KM estimates; Greenwood formula is used for CIs of KM estimates; CIs are point-wise intervals. The mean time to relapse (T=xx days) is the estimate associated with the area under the survival curve (KM mean survival time).
[7] p-value from log-rank test.
[8] Hazard ratio for placebo over iloperidone (95% CI) calculated using Cox's proportional hazards model. Notes:

1. The primary efficacy endpoint, time to relapse or impending relapse, is defined as the time from the first dose of double-blind study medication to the assessment at which the first-time relapse or impending relapse is identified. For patients not relapsing, the time to relapse is censored to the last DBRP period study visit, including the end of study visit, early termination visit, or unscheduled visit for the DBRP period.
2. Based on patients included in interim analysis and data cut-off date 17-Oct-2013.
* Significant p-value.

Figure 9: Study 2301. Kaplan-Meier plot of time to relapse or impending relapse - Double-Blind Relapse Prevention phase - interim analysis - FAS



DBRP = Double-Blind Relapse Prevention; FAS = Full Analysis set; ilo = iloperidone; pbo = placebo
Notes:
1. The primary efficacy endpoint, time to relapse or impending relapse, is defined as the time from the first dose of double-blind study medication to the assessment at which the first time relapse or impending relapse is identified. For patients not relapsing, the time to relapse is censored to the last DBRP period study visit, including the end of study visit, early termination visit, or unscheduled visit for the DBRP period.
2. Based on patients included in interim analysis and data cut-off date 07-Oct-2013.
* Significant p-value.

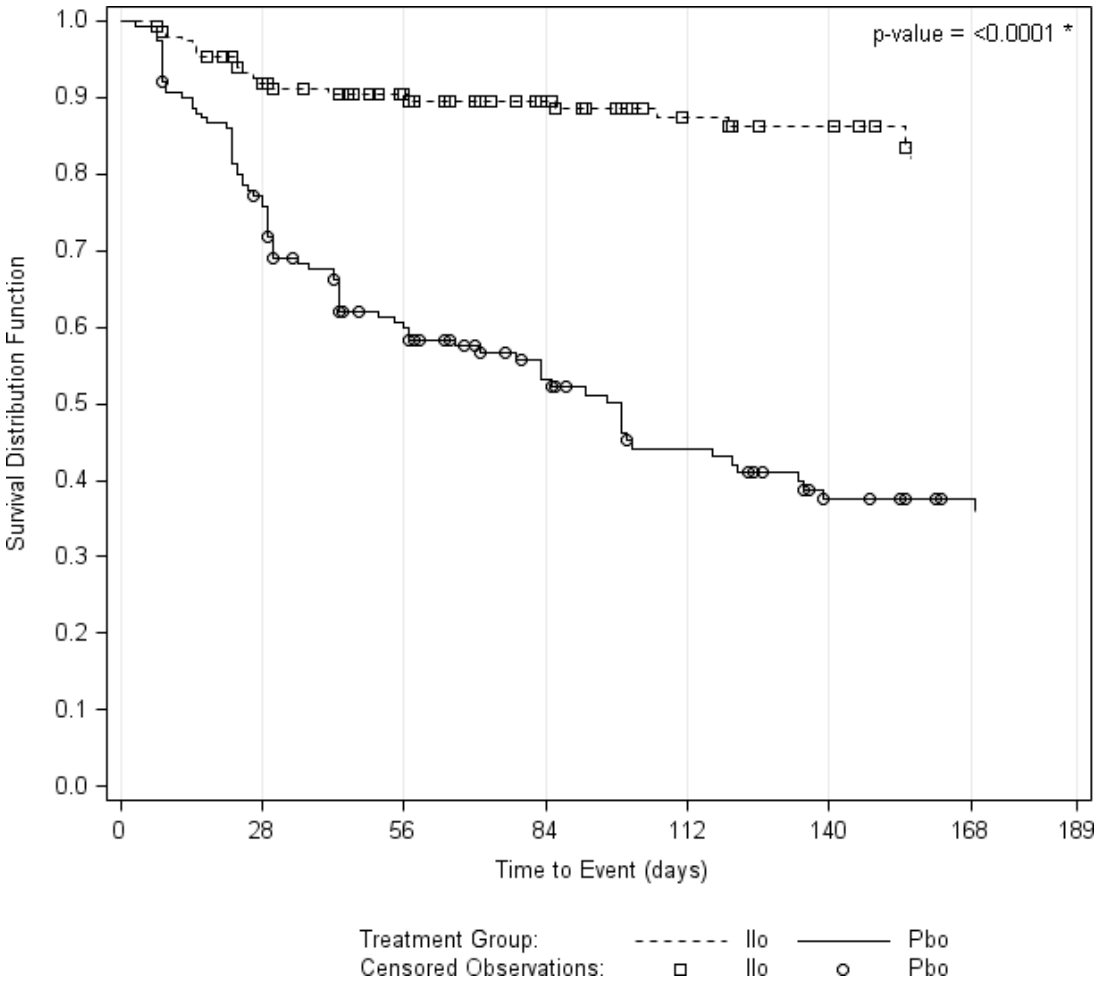
Table 31: Study 2301. Time to relapse or impending relapse (days), summary by time interval - Double-Blind Relapse Prevention phase - FAS

	Ilo N=151						Pbo N=150					
	Subjects at risk [2]		Subjects with event [3]			KM % est. without event [5]	Subjects at risk [2]		Subjects with event [3]			KM % est. without event [5]
Time interval [1] (days)	Start	End	N	%	n [4]	% (95% CI)	Start	End	N	%	n [4]	% (95% CI)
[1, 56]	151	112	14	9.3	14	90.4 (84.3, 94.2)	150	81	59	39.3	59	59.8 (51.4, 67.3)
[57, 112]	112	73	3	2.7	17	87.4 (80.3, 92.0)	81	43	17	21.0	76	44.1 (35.2, 52.6)
[113, 154]	73	65	1	1.4	18	86.2 (78.7, 91.2)	43	29	6	14.0	82	37.6 (28.8, 46.4)
[155, 182]	65	44	3	4.6	21	82.1 (73.3, 88.3)	29	15	1	3.4	83	36.0 (27.1, 45.0)
Mean time to relapse						(T=140 Days)						(T=95 Days)
Relapse Rate (95% CI) [6]						17.9 (11.7, 26.7)						64.0 (55.0, 72.9)
p-value [7]						<0.0001 *						
Hazard Ratio (95% CI) [8]						5.2 (3.2, 8.4)						

DBRP = Double-Blind Relapse Prevention; est. = estimate; FAS = Full Analysis Set; ilo = iloperidone; KM = Kaplan-Meier; pbo = placebo
[1] Day 1 = date of randomization.
[2] Start: immediately prior to the start time of the interval; End: immediately prior to the end time of the interval.
[3] Within the time-interval, denominator for rate is number of patients at risk immediately prior to the start time of the interval.
[4] n = Number of patients with event up to and including the end time of the interval.
[5] KM % estimates relate to the end time of the interval. KM estimates are displayed; Greenwood formula is used for CIs of KM estimates; CIs are point-wise intervals.
[6] Relapse Rate and 95% CI relate to the end time of the [155, 182] interval. Relapse rate estimates are calculated as: 100% - KM estimates; Greenwood formula is used for CIs of KM estimates; CIs are point-wise intervals. The mean time to relapse (T=xx days) is the estimate associated with the area under the survival curve (KM mean survival time).
[7] p-value from log-rank test.
[8] Hazard ratio for placebo over iloperidone (95% CI) calculated using Cox's proportional hazards model. Notes:

1. The primary efficacy endpoint, time to relapse or impending relapse, is defined as the time from the first dose of double-blind study medication to the assessment at which the first time relapse or impending relapse is identified. For patients not relapsing, the time to relapse is censored to the last DBRP period study visit, including the end of study visit, early termination visit, or unscheduled visit for the DBRP period.
* Significant p-value.

Figure 10: Study 2301: Kaplan-Meier plot of time to relapse or impending relapse - Double-Blind Relapse Prevention phase - FAS



Note: The primary efficacy endpoint, time to relapse or impending relapse, is defined as the time from the first dose of double-blind study medication to the assessment at which the first time relapse or impending relapse is identified. For patients not relapsing, the time to relapse is censored to the last DBRP period study visit, including the end of study visit, early termination visit, or unscheduled visit for the DBRP period.
*Significant p-value.

Results for the secondary endpoint change in PANSS total score from DBRP baseline to RP completion are shown in Table 32.

Table 32. Study 2301. Positive and Negative Syndrome Scale (PANSS Total Score), change from DBRP baseline and ANCOVA - DBRP phase - FAS (LOCF data)

Visit	Ilo. N=151	Pbo. N=150
DBRP Baseline		
N	151	150
Mean (SD)	55.5 (10.76)	55.1 (10.11)
Median	59.0	58.0
Minimum	31	31

Visit	Ilo. N=151	Pbo. N=150	
Maximum	73	70	
RP Completion			
N	150	149	
Mean (SD)	56.8 (14.86)	68.5 (19.49)	
Change From DBRP Baseline to RP Completion			
N	150	149	
DBRP Baseline Mean (SD)	55.6 (10.76)	55.2 (10.08)	
Mean (SD)	1.2 (10.09)	13.3 (15.20)	
Adj. Change Mean (SE)	1.1 (1.12)	12.4 (1.15)	p <0.0001 *

Adj. = adjusted; ANCOVA = analysis of covariance; DBRP = Double-Blind Relapse Prevention; FAS = Full Analysis set; ilo = iloperidone; LOCF = last observation carried forward; PANSS = Positive and Negative Syndrome Scale; pbo = placebo
Notes:
1. DBRP baseline is defined as the last available assessment prior to the first dose of double-blind study medication.
2. Change from DBRP baseline is calculated as post value minus DBRP baseline value. A negative change indicates improvement.
3. P-value is based on an ANCOVA model with treatment and site as main effects and DBRP baseline as a covariate.
4. Adjusted change is the least squared mean change obtained from the ANCOVA model.
5. RP Completion visit includes observations from last visit during DBRP period for patients who completed the study or RP Completion visit for patients who discontinued the DBRP phase and not included in previous scheduled visit.
* Significant p-value.

CGI-I

At the last visit of the double-Blind Relapse Prevention phase, the median global improvement rating was 3.0 (i.e., minimally improved) for the iloperidone treatment group and 5.0 (i.e., minimally worse) for the placebo treatment group. The adjusted mean was nominal significantly lower by ANOVA in the iloperidone treatment group (3.1) compared with the placebo treatment group (4.2; nominal p <0.0001). The percentage of patients with a global improvement rating of 4 (i.e., no change) at the last visit of the DBRP phase was nominal significantly higher in the iloperidone treatment group (30.7%) compared with the placebo treatment group (20.3%; nominal p <0.0001). At the last visit of the DBRP phase, the majority of patients in the iloperidone treatment group had improved (score < 4), and the majority of patients in the placebo treatment group had worsened (score > 4).

CGI-S

At the last visit of the double-Blind Relapse Prevention phase, the median score was 3.0 (i.e., mildly ill) for the iloperidone treatment group and 4.0 (ie, moderately ill) for the placebo treatment group. The majority of patients in the iloperidone treatment group were mildly ill or better (score ≤ 3), and the majority of patients in the placebo treatment group were moderately ill or better (score ≤ 4). Two patients (1.8%) in the iloperidone treatment group and 21 patients (20.0%) in the placebo treatment group were markedly ill (score = 5).

Ancillary analyses

Upon request, the Applicant conducted a sensitivity analysis of the primary endpoint (Table 33).

Table 33: Time to Relapse or Impending Relapse (days) Summary by Time Interval Double-Blind Relapse Prevention Phase - Randomized Population

	IlO N=153						Pbo N=150					
	Subjects at Risk[2]		Subjects with Event[3]		Cumulative Information		Subjects at Risk[2]		Subjects with Event[3]		Cumulative Information	
Time Interval[1] (days)	Start	End	n	%	n [4]	KM % est. without event [5] % (95% CI)	Start	End	n	%	n [4]	KM % est. without event [5] % (95% CI)
[1, 56]	153	112	41	26.8	41	73.2 (65.4, 79.5)	150	81	69	46.0	69	54.0 (45.7, 61.6)
[57, 112]	112	73	39	34.8	80	47.7 (39.6, 55.4)	81	43	38	46.9	107	28.7 (21.7, 36.0)
[113, 154]	73	65	8	11.0	88	42.5 (34.6, 50.1)	43	29	14	32.6	121	19.3 (13.5, 26.0)
[155, 182]	65	44	9	13.8	97	36.6 (29.0, 44.2)	29	15	10	34.5	131	12.6 (7.9, 18.5)
Relapse Rate						(T=125 Days)						(T=78 Days)
(95% CI) [6]						63.4 (55.8, 71.0)						87.4 (81.5, 92.1)
p-value [7]						<.0001 *						
Hazard Ratio												
(95% CI) [8]						1.9 (1.5, 2.5)						

[1] Day 1 = date of randomization.

[2] Start: immediately prior to the start time of the interval; End: immediately prior to the end time of the interval.

[3] Within the time-interval, denominator for rate is number of patients at risk immediately prior to the start time of the interval.

[4] n = Number of patients with event up to and including the end time of the interval.

[5] KM % estimates relate to the end time of the interval. Kaplan-Meier estimates are displayed; Greenwood formula is used for CIs of KM estimates; CIs are point-wise intervals.

[6] Relapse Rate and 95% CI relate to the end time of the [155, 182] interval. Relapse rate estimates are calculated as: 100% - Kaplan-Meier estimates; Greenwood formula is used for CIs of KM estimates; CIs are point-wise intervals. The mean time to relapse (T=xx days) is the estimate associated with the area under the survival curve (Kaplan-Meier mean survival time).

[7] p-value from log-rank test.

[8] Hazard ratio for placebo over iloperidone (95% CI) calculated using Cox's proportional hazards model. Notes:

1. The primary efficacy endpoint, time to relapse or impending relapse, is defined as the time from the first dose of double-blind study medication to the assessment at which the first time relapse or impending relapse is identified. For patients not relapsing, the time to relapse is censored to the last Double-Blind Relapse Prevention period study visit, including the end of study visit, early termination visit or unscheduled visit for the Double-Blind Relapse Prevention period.

2. Patients who discontinued the trial prematurely are considered as event.

* Significant p-value.

Study 3201: bipolar mania

Title: A multicentre, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of iloperidone for 4 weeks in the treatment of patients with acute manic episodes associated with bipolar I disorder.

Methods

Study Participants

The main inclusion criteria were

- Patients met the DSM-5 diagnosis of bipolar I disorder, manic or mixed type and had had the diagnosis for at least one year.
- Patients had at least one prior documented manic or mixed episode (with or without psychotic symptoms) that required treatment prior to screening.
- Patients had a CGI-S – Severity of Illness (Mania) score of at least 4 at baseline.
- Patients had a Young Mania Rating Scale (YMRS) total score ≥20 at screening and baseline.
- Patients had ≥ 4 on at least 2 of 4 YMRS items (irritability, speech, content, disruptive/aggressive behaviour).
- Patients had a Montgomery-Asberg Depression Rating Scale (MADRS) total score < 18.
- Patients were voluntarily hospitalized for current manic episode.

The main exclusion criteria were

- Patients who had a DSM-5 diagnosis of a psychiatric disorder other than bipolar I disorder that was the primary focus of treatment within the previous 6 months.
- Patients who had a diagnosis or history suggestive of chemical dependence according to DSM-5 criteria, or toxic psychosis in the preceding 6 months, or a clinical presentation possibly confounded by the use of recreational drugs or alcohol.
- Patients who suffered from other clinically significant medical conditions which could have been expected to progress, recur, or change to such an extent that they could have put the patient at special risk or bias the assessment of the clinical and mental status of the patient to a significant degree (e.g., second degree or higher hear block, a history of clinically significant valve disorders, NYHA Class II-IV heart failure, dilated, restrictive, or hypertrophic cardiomyopathy, severe or deteriorating cardiovascular disease, clinically relevant ECG abnormality (define as PR >240msec, QRS complex >110 msec, QTcF>500), severe obstructive lung disease, untreated thyroid disease, known active HIV or known active Hepatitis C infection, myocardial infarction within the past 6 months, insulin-dependent diabetes, acute electrolyte problems, etc.). This included any nonpsychiatric coexistent disease state that had not been maintained in a stable condition for at least 3 months prior to baseline.
- Patients who had known congenital long QT syndrome, Brugada syndrome, or other cardiac abnormality that would have increased the risk of ventricular arrhythmia.

Treatments

This was a randomised, double-blind, placebo-controlled phase-3-study to evaluate the efficacy and safety of iloperidone for 4 weeks in the treatment of patients with acute manic episodes associated with bipolar I disorder. It had two parallel arms and there was no active control group. Iloperidone dose was determined based on CYP2D6 genotype (poor or non-poor metaboliser). See Table 34.

All patients were to be hospitalized for a minimum of 3 weeks during the short-term, double-blind study (Days 1 to 28).

All patients who completed through day 28 of the short-term, double-blind phase had the option of continuing to the long-term, open-label phase for 1 year of treatment with iloperidone.

Table 34: Study 3201, study schema

Pre-randomization phase		**Short-term double-blind phase (b.i.d. dosing)**	
Screening period	Baseline visit	Titration period (mg/d)	Maintenance period (mg/d)
Days -7 to -1	Day 0	Days 1 to 7	Days 8 to 28
	iloperidone	non-poor metabolizers[a] 2→6→12→18→24→24→24	non-poor metabolizers [a] 24
		poor metabolizers[b] 2→6→12→12→12→12→12	poor metabolizers [b] 12
	placebo	placebo	placebo
	iloperidone	non-poor metabolizers[a] 2→6→12→18→24→24→24	non-poor metabolizers [a] 24
		poor metabolizers[b] 2→6→12→12→12→12→12	poor metabolizers [b] 12
	placebo	placebo	placebo

[a] CYP2D6 non-poor metabolizers (non-PMs) were titrated to 24 mg/d (12 mg bid) within 4 days and then maintained at the target dose for study duration.
[b] CYP2D6 poor metabolizers (PMs) were titrated to 12 mg/d (6 mg bid) within 2 days and then maintained at the target dose for study duration.

Regarding concomitant medication, any antipsychotic treatment taken prior to study enrolment was discontinued with the last dose on Day -1. Patients receiving stable doses for at least 6 weeks prior to study entry of medications with known CNS effects (e.g., anti-parkinsonian medications, beta-blockers, anxiolytics, or sedative/hypnotics), which were likely to interfere with study assessments, were prohibited during the study. Regarding rescue medication, *insomnia* was treated with zolpidem, *agitation/anxiety/severe restlessnes*s was treated with lorazepam and *EPS* were treated with benztropine.

Objectives

The primary objective was to evaluate the efficacy of iloperidone monotherapy compared to placebo in the treatment of adult patients with bipolar I disorder experiencing an acute manic or mixed episode.

There were several secondary objectives:

- To evaluate the efficacy of iloperidone monotherapy compared to placebo in the treatment of adult patients diagnosed with bipolar I disorder experiencing an acute manic or mixed episode as measured by improvements in the Clinical Global Impression of Severity (CGI-S).
- To evaluate the efficacy of iloperidone monotherapy compared to placebo in the treatment of adult patients diagnosed with bipolar I disorder experiencing an acute manic or mixed episode as measured by reduction in the Young Mania Rating Scale (YMRS) total score at each trial visit.
- To assess the rate of YMRS responders. A YMRS responder is defined as at least a 50% decrease from baseline in YMRS total score.

- To assess the efficacy of iloperidone monotherapy compared to placebo in improving clinical symptomatology in adult patients diagnosed with bipolar disorder, manic or mixed episodes after acute treatment as measured by CGI-C.
- To assess the efficacy of iloperidone monotherapy compared to placebo in improving clinical symptomatology in adult patients diagnosed with bipolar disorder, manic or mixed episodes after acute treatment as measured by MADRS.
- To assess the safety and tolerability of iloperidone compared to placebo in the treatment of adult patients in an acute manic or mixed episode of bipolar I disorder as measured by changes in vital signs and weight, laboratory analytes, electrocardiograms (ECGs), and the incidence and severity of TEAEs and extrapyramidal symptoms (EPS) using the Barnes Akathisia Scale, Simpson-Angus Scale, and the AIMS.

Outcomes/endpoints

The primary efficacy endpoint was the change from baseline to week 4 (Day 28) in the Young Mania Rating Scale (YMRS) total score at Week 4.

The secondary efficacy endpoints for the short-term double-blind phase were change from baseline in YMRS total score at each visit, YMRS response, and change from baseline in CGI-S, CGI-C, and MADRS at each visit.

Sample size

Based on a two-sided t-test with the 5% significant level, the planned sample size of 200 patients per arm (a total of 400 patients) was determined to provide around 90% power to detect a mean difference of 3.6 in YMRS (change from baseline at week 4) assuming a standard deviation of 11 in each treatment group.

Randomisation and blinding (masking)

Patients were randomized 1:1 to either iloperidone or placebo, stratified by country. Blocks contained at least 3 iloperidone CYP2D6 non-poor metabolizer units and at least 3 placebo units as well as at least 2 iloperidone CYP2D6 poor-metabolizer units (when available).

The study was double-blind. All study medication (iloperidone and matching placebo) for oral dosing was provided as an over-encapsulated tablet to ensure that they were identical in appearance (i.e., same size, colour, and shape).

Statistical methods

Analysis sets

The ITT population (ITT) was defined as any randomised patient that received at least one dose of study medication and completed at least one valid post-baseline efficacy measurement while on study medication.

Efficacy analysis

Only assessments that occurred within 3 days after last dose of medication in the short-term double-blind phase, but before the first dose of medication in the OLE phase if applied were considered.

The primary efficacy outcome was analysed using a mixed effect model repeat measurement (MMRM) under the missing-at-random assumption. The model included the fixed, categorical effects of treatment group, visit, treatment-group-by-visit interaction and pooled site as well as the fixed, continuous covariates of baseline score and the baseline score-by-visit interaction. The Kenward-Roger approximation was used to estimate denominator degrees of freedom. An unstructured (UN) covariance matrix was used.

Continuous secondary outcomes were analysed similarly as the primary outcome. Categorical outcomes were analysed by a Cochran-Mantel-Haenszel test with adjusting for sites.

To assess the robustness of the MMRM results to a possible violation of the missing-at-random assumption, a sensitivity analysis using a pattern-mixture model (PMM) based on non-future dependent missing value (NFDMV) restriction was performed. Under the NFDMV restriction, all missing observations were imputed using observed data with an assumption that all missing data occurred due to poor efficacy (one particular situation of missing not at random [MNAR]), so a pre-specified shift parameter = 1 as a sensitivity parameter was applied in missing data imputation. The completed dataset with the observed data and the imputed missing values were analysed with the same model as the primary analysis. As in a multiple imputation application, the imputation and analysis were performed at least 1000 times, and the inference of this sensitivity analysis was based on the combined estimates using the standard multiple imputation technique.

Interim analysis

No interim analyses were planned or conducted.

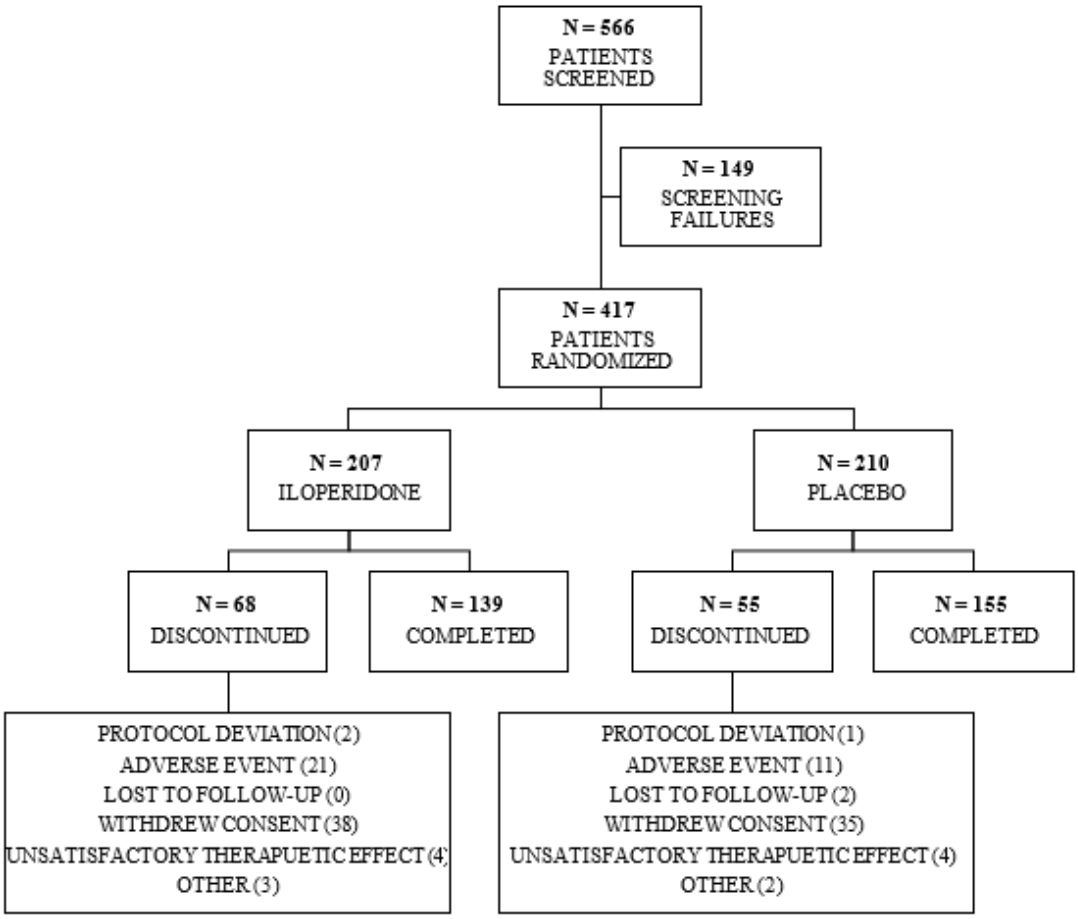
Multiplicity

To control the family-wise type I error at 5%, the key secondary outcomes were only be tested if the primary outcome was statistically significant. The key secondary outcomes were tested sequentially at two-sided 5% level.

Results

Participant flow

Figure 11: Study 3201. Participant flow



Recruitment

First patient enrolled: 04 April 2021. Last patient completed: 07 September 2022.

Conduct of the study

No amendments that might have affected the statistical robustness of the efficacy results were made while the trial was ongoing.

Baseline data

Baseline data is presented in Table 35 and Table 36.

Table 35: Study 3201. Demographic and baseline clinical characteristics by treatment IT Population

Characteristic	Iloperidone (N=198)	Placebo (N=194)	Total (N=392)
Age (years)			
n	198	194	392
Mean (SD)	42.9 (12.80)	43.5 (12.80)	43.2 (12.79)
Median	45.0	45.5	45.0
Range	18 to 65	18 to 65	18 to 65
Age group, n (%)			
<50 years old	124 (62.6)	120 (61.9)	244 (62.2)
≥50 years old	74 (37.4)	74 (38.1)	148 (37.8)
Sex, n (%)			
Male	113 (57.1)	105 (54.1)	218 (55.6)
Female	85 (42.9)	89 (45.9)	174 (44.4)
Race, n (%)			
American Indian or Alaska Native	1 (0.5)	2 (1.0)	3 (0.8)
Asian	0	3 (1.5)	3 (0.8)
Black or African American	59 (29.8)	55 (28.4)	114 (29.1)
Native Hawaiian or Other Pacific Islander	1 (0.5)	0	1 (0.3)
White	129 (65.2)	121 (62.4)	250 (63.8)
Other	8 (4.0)	13 (6.7)	21 (5.4)
Ethnic group, n (%)			
Hispanic or Latino	35 (17.7)	28 (14.4)	63 (16.1)
Not Hispanic or Latino	161 (81.3)	163 (84.0)	324 (82.7)
Not Reported	1 (0.5)	3 (1.5)	4 (1.0)
Unknown	1 (0.5)	0	1 (0.3)
Weight, kg			
n	198	194	392
Mean (SD)	85.6 (18.10)	87.1 (19.02)	86.3 (18.55)
Median	82.50	85.90	84.35
Range	49.0 to 139.9	49.6 to 166.2	49.0 to 166.2
Body Mass Index (BMI), kg/m^2			
n	198	194	392
Mean (SD)	29.0 (5.72)	29.5 (5.62)	29.3 (5.67)
Median	28.28	28.69	28.56
Range	18.3 to 41.2	18.5 to 41.57	18.3 to 41.57
BMI group, n (%)			
<25kg/m2	53 (26.8)	46 (23.7)	99 (25.3)
25-30kg/m2	64 (32.3)	63 (32.5)	127 (32.4)
>=30kg/m2	81 (40.9)	85 (43.8)	166 (42.3)
Height, cm			
n	198	194	392
Mean (SD)	171.66 (9.66)	171.63 (9.78)	171.65 (9.70)
Median	171.00	171.05	171.00
Range	150.0 to 203.0	146.0 to 205.0	146.0 to 205.0
DSM-5 diagnosis, n (%)			

Characteristic	Iloperidone (N=198)	Placebo (N=194)	Total (N=392)
bipolar I disorder, manic type	154 (77.8)	163 (84.0)	317 (80.9)
bipolar I disorder, mixed type	44 (22.2)	31 (16.0)	75 (19.1)
CYP2D6 Metabolizer Status			
Non-poor metabolizer	183[a] (92.4)	183 (94.3)	366[a] (93.4)
Poor metabolizer	15 (7.6)	11 (5.7)	26 (6.6)

Table 36: Study 3201. Mean (standard deviation) baseline scores for efficacy variables by treatment – ITT Population

Variable	Iloperidone (n=198)	Placebo (n=194)	Total (n=392)
YMRS total score	29.2 (5.27)	28.8 (4.64)	29.0 (4.97)
CGI-S score	4.60 (0.71)	4.60 (0.70)	4.60 (0.70)
MADRS score	10.2 (3.66)	9.9 (3.95)	10.0 (3.80)

Previous hospitalization for psychotic disorder was reported for 76.0% of the ITT population (71.7% and 80.4% of the iloperidone and placebo patients, respectively). The number of prior hospitalizations was most commonly between 1 and 5 (52.8 % of the ITT population), however patients with 6-10 prior hospitalizations were seen more often in the placebo group (22.2%) than the iloperidone group (12.6%). The proportions of patients having 11 or more previous hospitalizations for psychotic disorder were similar among both treatment groups.

Numbers analysed

See Figure 11.

Outcomes and estimation

Primary outcome: a statistically significantly greater reduction from baseline in YMRS score was demonstrated by the iloperidone group compared with placebo at Day 28, see Figure 12.

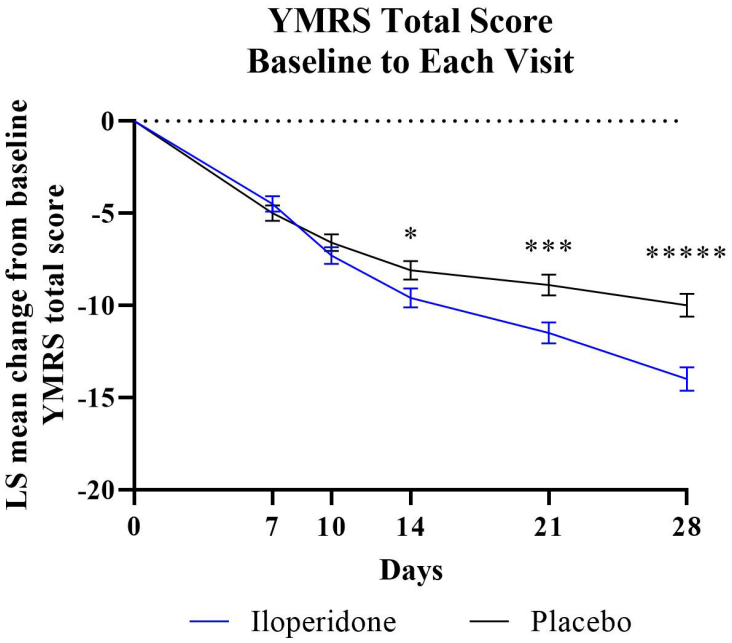
Figure 12: Study 3201: Primary Efficacy Variable (MMRM Analysis) – ITT Population

Timepoint	Iloperidone (n=198) [b]	Placebo (n=194) [b]	Difference [c] (95% CI) [b]	p-value [b]
YMRS Total Score, Day 28 (change from baseline) [a]	-14.0 (0.64)[c,d]	-10.0 (0.63)	-4.0 (-5.70, -2.25)	0.000008

MMRM = Mixed Model Repeated Measures. CI = Confidence Interval. LS = Least Squares. YMRS = Young Mania Rating Scale.
The YMRS total score is calculated by taking the sum of the 11 items with a total possible score of 0 (best) to 60 (worst). If the score of any item is missing, the total score is set to missing.
[a] Baseline is defined as the latest non-missing observation across all the visits in the Screening Phase before the study drug begins.
[b] LS means, CIs, and p-values are based on mixed-effects model for repeated measures (MMRM) model with fixed, categorical effects of treatment group, visit, treatment group-by-visit interaction and pooled site as well as the fixed, continuous covariates of baseline score and the baseline score-by-visit interaction.
[c] Difference between Iloperidone and Placebo.

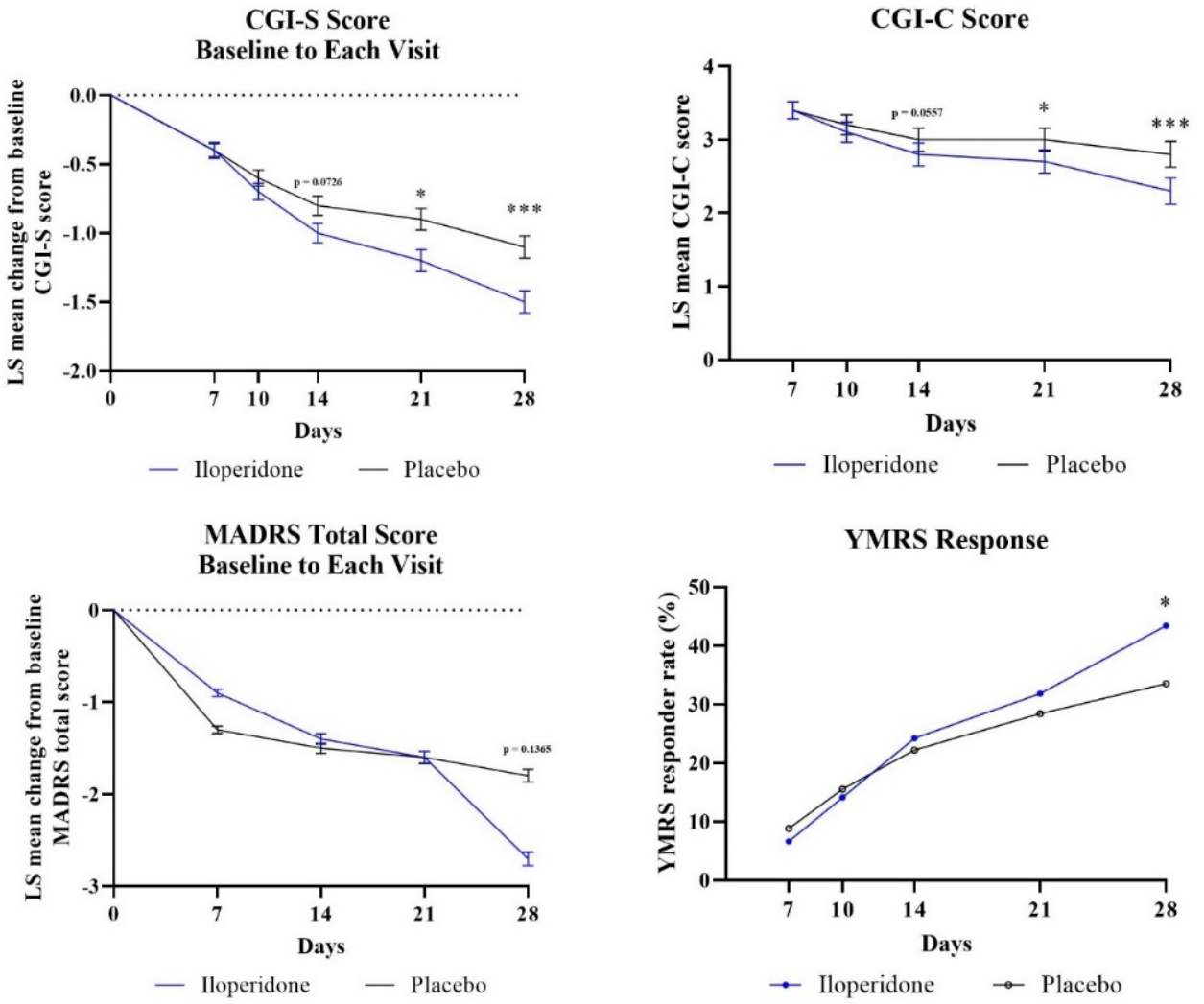
The secondary efficacy outcomes for the short-term double-blind phase were change from baseline in YMRS total score at each visit such as week 1 (Day 7), Day 10, week 2 (Day 14) and week 3 (Day 21), YMRS response, and change from baseline in CGI-S, CGI-C, and MADRS. The YMRS change from baseline to each visit is shown in Figure 13. Secondary efficacy endpoints are summarized in Figure 14.

Figure 13: Study 3201. YMRS Total Score: LS Mean Change from Baseline to Each Visit – ITT



Data shown are LS mean change from baseline. Error bars represent standard error for each data point. p-values (*, p<0.05; **, p<0.01; ***, p<0.001; ****, p<0.0001; *****, p<0.00001) are based on mixed-effects model for repeated measures (MMRM) model in ITT population.

Figure 14: Study 3201. Summary of secondary Efficacy Measures – ITT Population



CGI-S and MADRS are shown as LS mean change from baseline to each visit. CGI-C LS mean scores are shown for each visit measured. CGI-S, CGI-C, and MADRS data were calculated using mixed-effects model for repeated measures (MMRM) model in ITT populations. CGI-S, CGI-C, and MADRS error bars represent standard error (SE) for each plotted LS mean data point. YMRS Response is calculated in the LOCF population as the percentage of patients who achieved ≥50% reduction in YMRS Total Score on a given evaluation day. p-values represent iloperidone versus placebo (*, p<0.05; **, p<0.01; ***, p<0.001; ****, p≤0.0001).

Several secondary endpoints were evaluated. For *change from baseline in YMRS total score at each visit*, the iloperidone treatment groups separated from the placebo group with nominal statistical significance at day 14. The reduction compared to placebo was -1.4 points. *YMRS response* was defined as the percentage of patients who achieved ≥50% reduction in YMRS Total Score. At week 4, this was achieved for 43.4% of patients in the iloperidone group and 33.5% of patients in the placebo group, nominal p-value 0.0248.

In the MMRM analysis, a nominally significantly greater *reduction (improvement) from baseline in CGI-S* was demonstrated by the iloperidone group compared with placebo at Day 21 (-1.2 and -0.9, respectively, p=0.0146) and at study endpoint (-1.5 and -1.1 for iloperidone and placebo, respectively, at Day 28, p=0.0005).

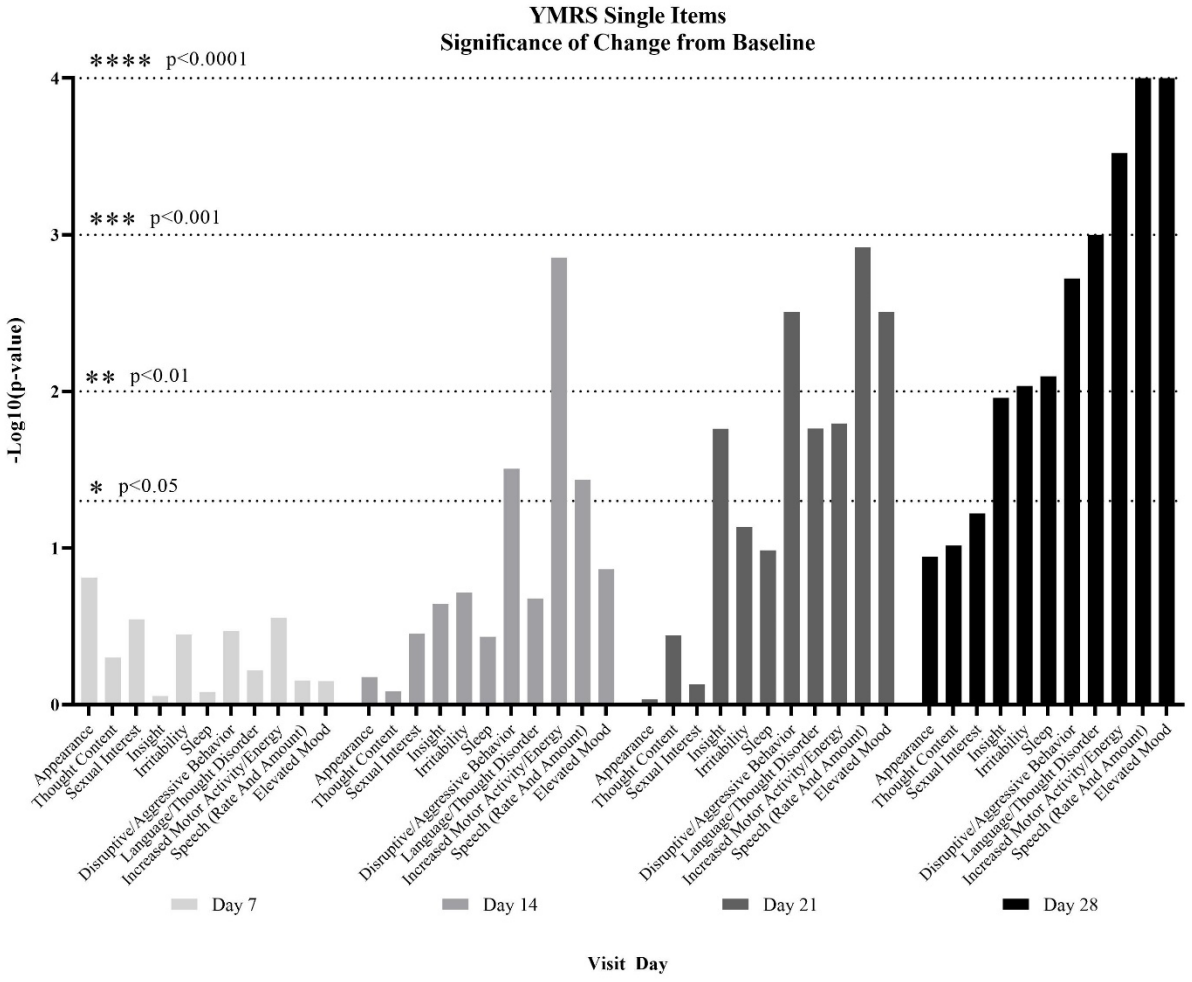
The *change in depressive symptoms from baseline to week 4*, as measured with the MADRS showed no nominally significant difference between iloperidone and placebo, with a mean reduction by 2.7 and 1.8 points in iloperidone and placebo group, respectively.

Ancillary analyses

Subgroup analyses by country, sex, race, age, and baseline severity were explored for the primary endpoint, change from baseline to endpoint (Day 28) in YMRS total score, using MMRM Model in the ITT population. Reductions in YMRS total score at Week 4 (Day 28) were generally similar in each subgroup evaluated.

Post hoc efficacy analysis was performed for the reductions from baseline in YMRS single items at each treatment week, see Figure 15.

Figure 15: Study 3201. YMRS Single Item Change from Baseline to Weeks 1, 2, 3, and 4 – ITT Population



-Log10(p-value) shown for each single item. p-values represent iloperidone vs placebo and are based on mixed-effects model for repeated measures (MMRM) model with fixed, categorical effects of treatment group, visit, treatment group-by-visit interaction, and pooled site as well as the fixed, continuous covariates of baseline score and the baseline score-by-visit interaction.

Upon request, the Applicant performed a sensitivity analysis of the primary endpoint (Table 37).

Table 37: Analysis of Change from baseline to Week 4 (Day 28) in YMRS Total Score using MMRM Model. Randomized Population (including data after premature treatment discontinuation)

Visit Statistic	Iloperidone (N=205)	Placebo (N=207)
Change from baseline to Visit 7 - Double Blind Day 28		
n	205	207
LS Mean	-13.03	-9.83
p-value	<.0001	<.0001
LS Mean Difference	-3.21	
p-value	0.0004	

Notes: Results are from MMRM model with post-baseline missing data imputed using jump-to-reference imputations (1000 imputations) and summarized using Rubin's rules.

Assessment comment: Confidence intervals were removed from the table because they contained a typographic error (the upper and lower confidence limits were identical).

2.6.5.3. Clinical studies in special populations

No subgroup analyses or clinical studies in special populations were performed for indications applied for. As for age groups, the main studies included subjects up to the age of 65 years. Some supportive short-term clinical studies included subjects up to the age of 69 years; these were placebo-controlled study ILP3007 Part 1 and risperidone-controlled ILP3007 Part 2 treating psychotic and behavioral symptoms in elderly patients with dementia (see safety under 2.6.8.6).

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable.

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

Not applicable.

2.6.5.6. Supportive study(ies)

Study **B202** was a Phase 2, prospective, randomized, double-blind, parallel-group, placebo-controlled, multi-centre study (11 centres in the US) conducted in hospitalized 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. The primary endpoint was not statistically different for the iloperidone 4 mg/d or 8 mg/d dose groups and placebo. The improvement in PANSS-N score [the subscale for negative symptoms] at Week 6 relative to baseline was nominally significant for the iloperidone 8 mg/d group compared to placebo (nominal p=0.025).

Studies **3001, 3002,** and **3003** were prospective, randomised, multicentre, double-blind, flexible-dose, parallel group, studies designed to compare maintenance of the antipsychotic effect over 46 weeks and to evaluate safety over 52 weeks of iloperidone (4-16 mg/d) and haloperidol (5-20 mg/d) in patients with schizophrenia or schizoaffective disorder. A fixed titration schedule in the first week of the study was followed by flexible dosing that was designed to mimic clinical practice.

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. During the applicant's interactions with the European Medicines Agency (EMA), it was advised that efficacy analyses should focus on time to relapse. For this reason, the study protocols were amended to include a survival efficacy analysis of the combined data from studies ILP3001, ILP3002, and ILP3003 as primary endpoint.

2.6.6. Discussion on clinical efficacy

The applicant applied for marketing authorisation in the EU in 2011 for an indication in schizophrenia but decided to withdraw that application when it was clear from CHMP feedback that a long-term placebo-controlled relapse prevention study (maintenance withdrawal design) would be required. Following completion of the maintenance study, the applicant reapplied for marketing authorisation in 2015. The outcome of this application was a refusal of marketing authorisation.

In the current application, the applicant sought marketing authorisation for two indications:

- Treatment of schizophrenia in adults.

- Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults.

There are no new clinical trials to support the schizophrenia indication; the submitted trials were all included in the 2015 application. The bipolar indication is supported by one short-term study. The two indications are discussed separately below.

2.6.6.1. Schizophrenia

The proposed indication *treatment of schizophrenia in adults* is questioned based on the statistical robustness and clinical meaningfulness of the efficacy results in the short-term studies, as well as the clinical meaningfulness of the results of the relapse-prevention study (2301) in relation to the safety issues identified, see further in section 4 (benefit risk assessment) of this report.

Design and conduct of clinical studies

The dossier included 11 clinical trials that had a primary or secondary efficacy endpoint and that were conducted in patients with schizophrenia or schizoaffective disorder. The characterisation of these trials as "main" or "supportive" has varied across procedures, both from the applicant's perspective and between the Rapporteurs.

In the current procedure, the five placebo-controlled phase-3 trials are characterised as the main trials. Four of these trials (studies 3000, 3004, 3005 and 3101) were assessed as being of equal importance for the characterisation of short-term efficacy in the treatment of schizophrenia. The fifth trial (study 2301) characterised long-term efficacy/relapse prevention using a randomised withdrawal design.

Overall study design

The design of the short-term studies is adequate in terms of study duration (4-6 weeks), choice of placebo and active control and choice of efficacy endpoints. The patient population in studies 3000, 3004 and 3005 comprised patients who met the DSM-IV diagnoses of schizophrenia or schizoaffective disorder. This had been discussed during both scientific advice and the previous marketing authorisation applications.

The EMA *Guideline on clinical investigation of medicinal products, including depot preparations in the treatment of schizophrenia* does not mention schizoaffective disorder specifically, but states that "Schizophrenia with co-morbid symptoms [such as manic and depressive symptoms, anxiety or obsessive-compulsive symptoms], should be distinguished from other psychotic disorders." The Applicant argued that in an acute psychotic episode, the two conditions cannot be separated, and that they are treated in the same way, which is acknowledged. Whether schizoaffective syndrome as a medical condition can be separated in a nosologically meaningful way from schizophrenia has been a subject of discussion for the past 50 years. In the revision of the DSM-IV resulting in the DSM-5 in 2013, the schizoaffective diagnosis was found to have low interrater reliability and low stability over time in individual patients. The diagnostic criteria were revised to better reflect the chronic nature of the condition, and the schizoaffective diagnosis was maintained in the diagnostic manual.

As for psychiatric diagnoses in general, there are no known biomarkers or other more objective ways of separating schizophrenia from schizoaffective disorder. The distinction is made by a thorough assessment of the symptom pattern over time, putting high demands both on the patient's ability to remember and wish to share previous and current symptoms and on the attention given to such details over a prolonged period by doctors, nurses and other caregivers.

As the applicant argued that iloperidone is effective in treating both schizophrenia and bipolar disorder, it would be inconsistent to regard the short-term studies that include schizoaffective participants as less informative than the one study with only schizophrenia participants.

The inclusion and exclusion criteria used in the short-term studies are adequate for selecting the patient population. Notably, the exclusion criteria have changed over time, particularly, to become more detailed and specific regarding the exclusion of different cardiac disorders, including conditions affecting the QTc interval. Mandatory hospitalisation for prolonged periods of time has also been implemented in the later studies.

Three different active comparators have been used. As for haloperidol (study 3000), this was an established treatment at the time of the trial, approved for both schizophrenia and schizoaffective disorder. The titration period for haloperidol that was utilised in the study is actually not needed for the treatment of an acute exacerbation in a patient with a known psychotic disorder; an effective dose can be given already at day 1 of treatment. The fixed target dose (15 mg/day) is high according to European recommendations, both current versions and those in use in the late 1990s/early 2000s. Haloperidol is still used in emergency settings, but there are several other treatment options available.

As for risperidone (studies 3004 and 3005), this is an adequate comparator, although the doses used are at the higher end of the effective dose range. Similarly, the titration period for risperidone is not needed in treatment of an acute exacerbation in a patient with a known psychotic disorder; an effective dose can be given day 1 of treatment.

It is not clear whether the results for the comparators could have been disadvantaged by the implementation of this titration, but this issue is not further pursued because the study was not designed to show superiority or non-inferiority to the active comparator.

As for ziprasidone (study 3101) oral treatment with ziprasidone would not be a first-line treatment choice in an emergency setting. A titration period is recommended, and there is a dose-dependent risk of QT-prolongation. It has been given at the highest approved dose in this study.

In the main trials, iloperidone was studied in doses from 4 to 24 mg/day. No dose-response study was performed with fixed dose levels prior to the phase-3 trials which is a deviation from the product development guideline. Fixed doses, fixed-dose intervals and flexible doses have been studied in an exploratory fashion between individual studies which would not seem optimal for generating interpretable data.

The primary efficacy endpoint in all studies was the change from baseline to week 4 or 6 in PANSS total score, or a score derived from this score (the 18-item PANSS-derived BPRS). The PANSS is a well-established instrument for assessing the severity in positive, negative and general symptoms of a psychotic disorders, and it is recommended in the EMA guideline. The 18-item PANSS derived BPRS has less focus on negative and other symptoms less responsive to pharmacological treatment but is an acceptable alternative. There were multiple secondary efficacy endpoints measures of CGI-S, CGI-C, CDSS and PANSS/BPRS response. However, no instrument specifically assessing improvement of function was used.

The design of the randomised withdrawal study 2301 was appropriate to inform on long-term efficacy in patients who were stabilised on iloperidone. The inclusion and exclusion criteria were adequate. Regarding the definition of relapse/impending relapse, all criteria pertaining to an increase in symptoms of schizophrenia or increase in the level of care needed are adequate.

Estimands

The estimand framework was not used in any of the studies.

Sample size

Four of the 5 main trials adhered to the target sample size. The exception was the relapse-prevention trial (study 2301), which was an event-driven trial. The planned number of events was 104, but the protocol called for an interim efficacy analysis at 60 events. This interim analysis was performed when 68 events had occurred. Since the results showed a statistically significant reduction in relapses/impending relapses in the iloperidone group, the sponsor decided to stop the trial early for efficacy. When the trial was stopped, 104 events out of the planned 123 events had been observed.

Randomisation

The randomisation procedure was not clearly described in 4 of the studies (2301, 3000, 3004, and 3005), since information on stratification and blocking was lacking. However, this is a relatively minor issue, so it will not be further pursued.

For study 3101, the clinical study report referred to two different sets of randomised patients: 606 and 593 depending on whether patients who were randomised in error were or were not counted. Three of the patients who were randomised in error were screening failures, and 10 patients had already been randomised at another study site. The exclusion of these 13 patients was considered reasonable, but the 3 screening failures were included in a requested sensitivity analysis. The results were similar to the results of the primary analysis (data not shown in this report).

Pre-specification of the analyses

The statistical analyses were conducted as planned.

In the three trial that showed a statistically significant result on the primary endpoint (studies 3000, 3004, or 2301), there were no changes to the protocols that might have affected the statistical integrity of the efficacy results.

While study 3004 was ongoing, the primary endpoint was changed from the PANSS total score to the 18-item PANSS-derived BPRS. The reason for this change was that the results of study 3000 had indicated that the BPRS might be more sensitive in detecting treatment effects. The change is acceptable because it was made before unblinding. It is also reassuring that significant effects (with multiplicity adjustment) were detected for both PANSS total and PANSS-BPRS, so the change has not affected the interpretation of the results.

In study 3101, the primary analysis was to compare the efficacy of iloperidone 24 mg/d compared to placebo in the overall population. However, the trial also had a second primary objective, which was initially to compare the efficacy of iloperidone 24 mg/d in patients with the CNTF FS63Ter(-) genotype compared to patients with the CNTF FS63Ter(+) genotype. In a late protocol amendment, issued when 570 out of 606 patients had been randomised, this objective was changed to comparing 24 mg/d to placebo in the CNTF FS63Ter(-) genotype subgroup. This change is acceptable and appropriate because it was done before unblinding and, in contrast to the initial objective, it is a randomised comparison.

Premature study discontinuation and missing data

As shown in , the percentage of patients who prematurely discontinued follow up varied among the 5 main trials, but it was high in all of the trials. The differences between the arms were inconsistent – sometimes the discontinuation rate was higher in the iloperidone arm, sometimes it was higher in the placebo arm, and sometimes it was similar in the different arms. The two previous CHMP assessments of iloperidone also discussed the influence of study discontinuations and missing data on the results.

Table 38: Premature study discontinuation and missing data

Trial	Arms	Number of randomised patients	Number of patients who prematurely discontinued the trial	Missing data method
2301	Iloperidone (8-24 mg/d)	99	23 (23%)	Censoring
	Placebo	96	12 (13%)	
3000	Iloperidone 4 mg/d	121	69 (57%)	Last observation carried forward
	Iloperidone 8 mg/d	125	80 (64%)	
	Iloperidone 12 mg/d	124	72 (58%)	
	Haloperidol 15 mg/d	124	81 (65%)	
	Placebo	127	87 (69%)	
3004	Iloperidone 4-8 mg/d	153	79 (52%)	Last observation carried forward
	Iloperidone 10-16 mg/d	154	67 (44%)	
	Risperidone 4-8 mg/d	153	64 (42%)	
	Placebo	156	94 (60%)	
3005	Iloperidone 12-16 mg/d	244	113 (46%)	Last observation carried forward
	Iloperidone 20-24 mg/d	145	59 (41%)	
	Risperidone 6-8 mg/d	157	45 (29%)	
	Placebo	160	73 (46%)	
3101	Iloperidone 24 mg/d	295	102 (35%)	Mixed model for repeated measures (missing at random)
	Ziprasidone 16 mg/d	149	51 (34%)	
	Placebo	149	59 (40%)	
	Placebo	210	55 (26%)	

Assessors' table.

In study 2301, missing data were handled using censoring in the primary efficacy analysis, which means that discontinuation is assumed to be unrelated to the patients' risk of relapse. If this assumption is false, the results could be biased. The applicant was therefore asked to conduct a sensitivity analysis in which censored patients were counted as having had an endpoint event, which was considered to be a conservative method of handling the missing data. This sensitivity analysis showed a smaller effect estimate than pre-specified analysis (HR=1.9 versus HR=5.2). However, the effect was still statistically significant ($p<0.001$), so the results were considered statistically robust.

In three of the main trials (studies 3000, 3004, and 3005), missing data were handled using the last-observation-carried-forward method. This method is often not conservative (p-values tend to become

too low), and the last observation might be a poor estimate of a patient's final outcome. Sensitivity analyses were not requested for studies 3000 and 3005, as these studies failed show a statistically significant effect of iloperidone. For study 3004, however, the applicant was asked to conduct a sensitivity analysis with jump-to-reference multiple imputation, which was considered to be a reasonably conservative imputation method. This sensitivity analysis did not show a statistically significant effect, so the results of study 3004 were not considered statistically robust.

In study 3101, missing data were handled using a mixed model with repeated measures, which assumes that data are missing at random. If this assumption is false, it can lead to bias. The applicant was therefore asked to conduct a sensitivity analysis with jump-to-reference multiple imputation, which was considered to be a reasonably conservative imputation method. This sensitivity analysis did not show a statistically significant effect, so the results of study 3101 were not considered statistically robust.

Data observed 3 or more days after patients had prematurely discontinued study treatment were excluded from the analyses in 4 of the 5 main trials. The exception was the study of relapse prevention (study 2301). The applicant was asked to rerun the primary analyses of the two other successful studies (3004 and 3101) but include post-treatment-discontinuation data. The results were similar to the results of the primary analysis (data not shown in this report).

Analysis sets

The primary analyses of the 5 main trials were conducted in modified intention-to-treat sets, meaning that patients were excluded if they did not receive at least 1 dose of study treatment or did not have at least 1 post-baseline measurement. It is unclear if these exclusions could have had any influence on the results of the 3 trials which succeeded in showing statistically significant effects on their primary endpoints (studies 3004, 3101, and 2301). Therefore, the applicant was asked include all randomised patients in sensitivity analyses. The results were similar to the results of the pre-specified analyses (data not shown in this report).

Trial	Arms	Number of randomised patients	Number of patients excluded from the primary efficacy analysis
2301	Iloperidone (8-24 mg/d)	99	2 (2%)
	Placebo	96	0 (0%)
3000	Iloperidone 4 mg/d	121	8 (7%)
	Iloperidone 8 mg/d	125	11 (9%)
	Iloperidone 12 mg/d	124	9 (7%)
	Haloperidol 15 mg/d	124	10 (8%)
	Placebo	127	10 (8%)
3004	Iloperidone 4-8 mg/d	153	10 (7%)
	Iloperidone 10-16 mg/d	154	5 (3%)
	Risperidone 4-8 mg/d	153	7 (5%)
	Placebo	156	4 (3%)
3005	Iloperidone 12-16 mg/d	244	4 (2%)
	Iloperidone 20-24 mg/d	145	4 (3%)
	Risperidone 6-8 mg/d	157	9 (6%)
	Placebo	160	8 (5%)
3101	Iloperidone 24 mg/d	295	12 (4%)
	Ziprasidone 16 mg/d	149	5 (3%)
	Placebo	149	9 (6%)

Multiplicity

In study 2301, an interim efficacy analysis was conducted at a pre-specified, fixed alpha of 0.001 when 68 endpoint events had been observed. This number of events was slightly more than the 60 event pre-specified for the interim analysis in the protocol. A reanalysis at 60 events will not be requested because the p-value observed at 68 events is much less than the alpha of 0.001 (the p-value was <0.0001), so there is no indication that this slight delay in the interim analysis was an active, data-driven decision. The interim analysis is therefore adequately controlled for multiplicity. Since efficacy was declared at the interim analysis, no formal testing of efficacy is needed at the final analysis at 104 events.

In studies 3004 and 3005, multiplicity was controlled for the comparison of the two iloperidone arms to placebo using hierarchical testing. In study 3004, the original protocol stated that the Hochberg procedure would be used, but this was changed to a hierarchical testing strategy in a protocol amendment. This change had no impact of the conclusion of the trial, as efficacy would have been declared with either method.

In study 3101, multiplicity was controlled in the analysis of the primary endpoint because the pre-specified subgroup analysis of patients with the CNTF FS63Ter(-) genotype was only tested for efficacy if efficacy had first been demonstrated in the full study population.

The analyses of secondary endpoints were not controlled for multiplicity in the 3 main trials that demonstrated a significant effect (studies 2301, 3004, or 3101).

Efficacy data and additional analysis

Baseline data

Baseline data from the short- and long-term studies did not show any discrepancies between the treatment arms that are likely to have affected the efficacy results. The age distributions were representative of the target population; however, the minimum age for the first time being diagnosed with psychosis was remarkably low (**3** years of age being the lowest) which likely reflects differences in diagnostic practice over time and between countries. As the mean and median age at first diagnosis were in line with current understanding of the disorder and its usual age of onset, and all participants went through diagnostic evaluation prior to inclusion, this issue is not further pursued.

Results

Of the 4 short-term trials in schizophrenia, 2 trials had primary results that were statistically significant (studies 3004 and 3101) and 2 trials did not (3000 and 3005). Statistical significance was also seen in the primary analysis of the relapse-prevention/randomised-withdrawal trial (2301).

In study **3000**, the primary analysis was a comparison of the average results in the 8 and 12 mg/d dose arms to the placebo arm, and this comparison was not statistically significant (p-value: 0.065). A nominally significant result was seen when the 12 mg/d arm was compared to placebo, but the p-value would not have been statistically compelling even if it was type-1-error controlled (nominal p-value: 0.047). The mean (SD) change in PANSS-T score was 8.6 (19.6) points for the 12 mg/day arm compared to 4.1 (24.1), giving a difference between the means of 4.5 points. This is well below the suggested minimal clinically important difference (MCID) for PANSS.

Similarly, the primary analysis in study **3005** compared a 12-16 mg/d arm to placebo, which failed to show a significant difference (p-value: 0.090), but the trial showed a nominally significant difference when the 20-24 mg/d arm was compared to placebo (nominal p-value: 0.01). The difference between the mean changes on the BPRS of the 20-24 mg/d group and placebo group was 8.6-5.0=3.6 points.

The 18-item PANSS-derived BPRS does not seem to have an established MCID, but in one study linking the BRPS, the PANSS and the CGI, a percentage reduction of the BPRS by approximately 28 percentage points (range 27–30) reflected a reduction of the CGI severity score by one severity step, and a 10-points reduction corresponded roughly to minimal improvement. Considering this, a 3.6-point difference to placebo is of questionable clinical relevance.

Regarding the secondary endpoints in study **3000**, the proportion of patients who achieved ≥20% reduction relative to baseline on the PANSS-T was not nominally significantly different from placebo. Neither were any nominally significant differences seen between any of the iloperidone treatment groups and placebo in additional post-hoc analyses of treatment response defined as at least 30% or at least 40% reduction on the total PANSS score in schizophrenia patients only. However, the proportion of patients reaching clinical improvement on the CGI-C was nominally significant in the iloperidone 8 mg/d group at Weeks 4 and 6 and in the 12 mg/d group at Week 4 (LOCF dataset). For the haloperidol group, a nominally significant proportion of patients achieved clinical improvement compared with placebo from Week 2 onward.

Regarding the secondary endpoints of study **3005**, the proportion of patients with a 20% or greater improvement over baseline for BPRS was nominally statistically significant different between both iloperidone groups and placebo in week 3 only. On the other hand, for risperidone, the percentage of patients achieving at least 20% improvement reached nominal statistical significance relative to placebo by Week 2 and continued through Week 6. The reduction in PANSS total score from visit to visit was nominally statistically significantly greater in the iloperidone 12-16 mg/d group at Weeks 3 through 5 for the iloperidone 20-24 mg/d group, this was seen at Weeks 3 through 6. In the risperidone group a nominally statistically significantly greater reduction compared to placebo was achieved from Weeks 1 through 6.

In the additional post-hoc responder analyses in schizophrenia patients only, 25.3% of patients in the 12-16 mg iloperidone group had at least a 30% reduction on the BPRS at week 6 compared to 13.3 % in the placebo group (nominal p-value 0.040). In the 20-24 mg group 22.5% were responders at week 6 (nominal p-value 0.052). The risperidone treatment group separated from the placebo group at week 3, with 34.5% of patients being responders at week 6 (nominal p-value 0.002). Separate analyses of treatment response in schizophrenia patients with at least two weeks of treatment were also performed. In the 12-16 mg iloperidone group, 33.6 % of these patients had at least a 30% reduction on the BPRS at week 6 compared to 16.9 % in the placebo group (nominal p 0.023). In the 20-24 mg group 27.8% were responders at week 6 (nominal p 0.030). In the risperidone treatment group 38.3% of patients were responders at week 6 (nominal p 0.005).

In study **3004**, the pre-specified primary endpoint was the change in the 18-item BPRS total score. The mean difference between the iloperidone 10-16 mg group and the placebo was 4.9, which was statistically significant (p=0.001). However, there were a lot of missing data, so the applicant was asked to conduct a sensitivity analysis with jump-to-reference multiple imputation, which was considered to be a reasonably conservative imputation method (the pre-specified method of handling missing data was the last-observation-carried-forward method, which was considered unreliable). In this sensitivity analysis, the point estimate decreased from 4.9 to 2.99, and the effect was no longer statistically significant (p=0.0696), so the primary efficacy results of study 3004 were considered non-robust.

The prespecified secondary endpoint of treatment response defined as the proportion of patients with ≥20% improvement on the 18-item BPRS showed no nominally significant difference between any of the iloperidone groups and placebo. In the additional post-hoc analyses of treatment response defined as at least 30% or at least 40% reduction on the 18-item BPRS score compared to baseline in schizophrenia patients only, no nominally significant differences in favour of iloperidone treatment

were demonstrated in any of the treatment groups compared to placebo regarding the proportion of responders.

Altogether, the results for the primary endpoint were considered not statistically robust considering the results of performed sensitivity analyses. In addition, the clinical relevance of the difference compared to placebo was questioned in relation to the safety issues identified, see section 3. Further, the responder analyses were negative, and the TEAE profile indicated limited efficacy.

In study **3101**, which was conducted in schizophrenia patients only, the primary endpoint was the change in the PANSS-T score. The mean difference between the iloperidone group and the placebo group was -4.92, which was statistically significant ($p<0.01$). However, there were a lot of missing data, so the applicant was asked to conduct a sensitivity analysis with jump-to-reference multiple imputation, which was considered to be a reasonably conservative imputation method (the pre-specified method of handling missing data was a MMRM model assuming that data were missing at random, which was considered unrealistic). In this sensitivity analysis, the point estimate decreased from -4.92 to -3.05, and the difference was no longer statistically significant ($p=0.09$), so the primary efficacy results of study 3101 were considered non-robust.

As in the previous studies, even if the primary efficacy results had been statistically robust, the magnitude of effect in study 3101 was small, well below the suggested MCID for PANSS. Further, the onset of effect was slow, with the iloperidone group separating from the placebo group only after three weeks of treatment. This is a considerable drawback in terms of the usefulness of the product for the treatment of acute exacerbations of schizophrenia.

The prespecified secondary endpoint of treatment response defined as the proportion of patients with ≥20% improvement on the PANSS-T score showed no nominally significant difference between iloperidone and placebo. Neither was this convincingly shown in the additional post-hoc analyses of treatment response defined as at least 30% or at least 40% reduction on the PANSS total score compared to baseline. In the iloperidone group, 15.9% of patients had at least a 30% reduction on the PANSS-T at day 28 compared to 12.1 % in the placebo group (nominal p 0.404).

Altogether, the results for the primary endpoint in study 3101 were not statistically robust, and the difference compared to placebo is small and the time to onset is slow put in relation to the safety issues identified, see section 3. The responder analyses also indicate very limited efficacy.

In the randomised withdrawal study **2301**, the primary endpoint was met as there was a statistically significantly longer time to relapse/impending relapse in the iloperidone group compared to the placebo group, mean time 139 and 71 days respectively. The relapse rate was lower in the iloperidone group than in the placebo group, 20.4% vs 63.4% in the initially presented analyses, which is in line with previous research findings on relapse rates on and off antipsychotic treatment.

The primary efficacy results of study 2301 were also statistically robust. The hazard ratio for the primary endpoint (time to relapse/impending relapse) decreased from 5.2 to 1.9 when missing data were handled using a sufficiently conservative imputation method (failure imputation instead of censoring). However, the effect was still statistically significant ($p<0.001$).

The secondary endpoints were all in favour of iloperidone treatment over placebo, but as explained above, these endpoints were not adequately controlled for multiplicity, so the secondary endpoint results are inconclusive.

The results for the primary endpoint in study 2301 indicate that patients who have been stabilised on iloperidone have a more favourable outcome regarding relapse if they continue to take iloperidone than if they do not take any antipsychotic medication at all.

2.6.6.2. Bipolar disorder

The proposed indication *treatment of acute manic or mixed episodes associated with bipolar I disorder in adults* is questioned on the clinical meaningfulness of the effect size and the time to onset of effect put in relation to the safety issues identified.

Design and conduct of clinical studies

Overall study design

Study **3201** was a double-blind, placebo-controlled study to evaluate the efficacy and safety of iloperidone for 4 weeks in the treatment of patients with acute manic episodes associated with bipolar I disorder. There was no active control group. The iloperidone dose was determined based on CYP2D6 genotype with poor metaboliser receiving 12 mg/day and non-poor metabolisers receiving 24 mg/day. However, it is not clear whether the conducted genotyping studies are sufficiently up to date and comprehensive to conclude that this recommendation is appropriate, and there was no proposed requirement that patients should be genotyped before starting treatment **.** The applicant was requested to discuss the feasibility of conducting evaluation of CYP2D6 metabolize status in EU countries before treatment initiation in the proposed indications, especially in acute treatment, but has not provided a satisfactory response. Considering the negative benefit-risk balance, this issue is not further pursued.

Patients who completed the 28-day short-term, double-blind phase of the trial had the option of continuing to a long-term, open-label phase with 1 year of treatment with iloperidone.

The study included patients who met the DSM-5 diagnosis of bipolar I disorder, manic or mixed type, and had had the diagnosis for at least one year. The primary efficacy endpoint was the change from baseline to week 4 (Day 28) in the Young Mania Rating Scale (YMRS) total score at Week 4. There were multiple secondary efficacy endpoints measures of MADRS, CGI-S, CGI-C, and YMRS response.

Although the patient population was adequately selected, as were the efficacy endpoints, the overall design of the study is not in line with the recommendation of the current EMA guideline (CPMP/EWP/567/98), nor the draft of the updated version. Maintenance of effect during the episode has to be shown in a study which, according to guidelines, should be 12 weeks with an active comparator and include assessment of the occurrence of switching to depression. The open-label extension study cannot compensate for this shortcoming.

Sample size

The trial adhered to its target sample size.

Pre-specification of the analysis

The statistical analyses were conducted as they were pre-specified. No changes were made to the protocol while the trial was ongoing that could have affected the statistical integrity of the results.

Premature study discontinuation and missing data

The percentage of patients who prematurely discontinued follow up was higher in the iloperidone arm (33%, n=68) than in the placebo arm (26%, n=55). The resulting missing data were handled using a mixed model with repeated measures, which assumes that the data are missing at random.

If the missing-at-random assumption is false, it can lead to bias. Although the Applicant conducted a sensitivity analysis using a pattern-mixture model with a pre-defined shift parameter of 1, it was

unclear whether this sensitivity analysis was sufficiently conservative. The Applicant was therefore asked to conduct an additional sensitivity analysis with jump-to-reference multiple imputation of missing data, which was considered to be a sufficiently conservative method. This sensitivity analysis showed a smaller effect estimate on the primary endpoint (change in YMRS total score to week 4) than the pre-specified analysis did (-3.2 versus -4.0). However, the effect was still statistically significant ($p<0.001$), so the primary the primary efficacy results were considered statistically robust.

The statistical analysis plan suggested that data observed after a patient prematurely discontinued treatment were excluded from the primary efficacy analysis. The Applicant was therefore asked to run a sensitivity analysis in which post-treatment-discontinuation data observed during the double-blind part of the trial were included. The results of this sensitivity analysis were similar to the results of the pre-specified analysis (data not shown in this report).

Analysis sets

The primary analysis was conducted in a modified intention-to-treat set, meaning that 4% (n=9) of patients in the iloperidone arm and 8% (n=16) in the placebo arm were excluded from the analysis because they did not receive at least 1 dose of study treatment or have at least 1 post-baseline measurement. The Applicant was asked to include all randomised patients in a sensitivity analysis. The results of this sensitivity analysis were similar to the main results (data not shown in this report).

Multiplicity

According to the statistical analysis plan, the analysis of the key secondary endpoints in study 3201 was supposed to be controlled for multiplicity using hierarchical testing. However, the key secondary endpoints were not specified, and the secondary endpoints are ordered differently in the protocol and the statistical analysis plan. This makes the multiple testing strategy ambiguous, which means that multiplicity has not been adequately controlled for the two secondary endpoints 'CGI-Severity score' and 'CGI-Change score' whose p-values are less than 0.05.

Efficacy data and additional analyses

Participant flow and baseline data

In total, 417 patients were randomised to the study.

The baseline data did not show discrepancies between the treatment arms that are likely to have affected the efficacy results. There was a slight majority of men in the trial population, which does not quite reflect the target population, but it is acceptable from an efficacy assessment point of view.

The YMRS and CGI-S ratings corresponded to moderate mania, with some patients having a total YMRS score corresponding to the lower range of severe mania.

The proportion of poor metabolisers was the same as one would assume in the EU population, around 7%.

Primary and secondary efficacy results

After the requested sensitivity analysis described above, the reduction in YMRS score from baseline to day 28 was still statistically significantly greater in the iloperidone group compared to the placebo group ($p > 0.001$), but the effect estimate decreased from a reduction by 4.0 to 3.2 points. While the primary endpoint of the study was met, the effect size of iloperidone treatment seems modest (see further in section 3), and the onset is slow, neither of which are appropriate in the sought treatment setting of an acute manic or mixed episode. Apart from reducing symptom severity, the time to onset

of action is an important aspect of treatment of an acute manic or mixed episode. In a review comparing the time to onset for different antipsychotics, haloperidol, risperidone, and olanzapine had onsets appearing in 2-6 days. In an individual patient data meta-analysis, it was suggested that clinicians should reconsider their treatment strategy if patients failed to respond early.

Subgroup analyses by country, sex, race, age, and baseline severity were explored for the primary endpoint, change from baseline to endpoint (Day 28) in YMRS total score. Reductions in YMRS total score at Week 4 (Day 28) were generally similar in each subgroup evaluated.

The secondary efficacy endpoints for the short-term double-blind phase included change from baseline in YMRS total score at each visit such as week 1 (Day 7), Day 10, week 2 (Day 14) and week 3 (Day 21), YMRS response, and change from baseline in CGI-S, CGI-C, and MADRS.

For change from baseline in YMRS total score at each visit, the iloperidone treatment groups separated from the placebo group with nominal statistical significance in treatment week 2, but the reduction in YMRS score compared to placebo (-1.4 points) is of uncertain clinical relevance, even if it were formally statistically significant.

As for the other secondary endpoints, the difference compared to placebo is small and appears at treatment week 3-4. There is no indication that there is an increase in depressive symptoms in the iloperidone group.

Therefore, the clinical relevance of both the primary and secondary findings is questionable.

2.6.7. Conclusions on the clinical efficacy

2.6.7.1. Schizophrenia

The results of the short-term efficacy trials were not statistically robust, and there were major clinical deficiencies in the efficacy results. This precludes a favourable conclusion on the efficacy of iloperidone for the indication of treatment schizophrenia in adults.

2.6.7.2. Bipolar disorder, acute manic or mixed episodes

Major clinical deficiencies and uncertainties have been identified in the phase-3 trial. These shortcomings preclude a favourable conclusion on the efficacy of iloperidone for the indication of treatment of acute manic or mixed episodes associated with bipolar I disorder in adults.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

More than 40 clinical studies have been conducted with iloperidone, but the integrated summary of safety builds on 12 clinical studies. In the previous application in 2015 the safety database consisted of a pooling of 11 studies (4540 patients exposed to iloperidone). In the current application the study 3201 (bipolar mania) has been added with 207 patients exposed to iloperidone during the placebo-controlled phase and 182 exposed during the OL long-term extension phase. In the current application the integrated safety database consists of 4852 patients exposed to iloperidone. The major pooled dataset (Study Group 1) includes therapeutic studies of patients with any iloperidone exposure enrolled into studies in all phases (controlled and uncontrolled) of all 12 studies combined. Study group 2

consists of 5 placebo-controlled studies, including the key study for the schizophrenia indication (3101) and the key study for the mania indication (3201).

Long-term treatment

In the current pooled data, 1506 patients were treated with iloperidone for over 6 months, and 857 patients were treated for over one year. Of these, 171 patients received a dose of 20-24 mg/d for >6 months and 80 patients for >12 months. The number of patients exposed long-term to the highest dose is consequently low.

Age and sex distributions

There are no subjects >69 years of age included in the studies presented. Roughly 1/3 of the patients were female.

Inclusion/exclusion criteria in the clinical trials

Patients with relevant preexisting cardiovascular disease, including baseline ECG abnormalities, were excluded from the main clinical trials. To be included, patients were also required to be willing to be hospitalized for varying periods during the initial phases of treatment. In the key study 3101 all patients were hospitalized during the first 4 weeks of the short-term double-blind study. This is a strong risk mitigation measure, not adequately reflected in the applicant's discussion or proposed risk minimisation measures. The proposed warnings are too brief and unspecific regarding treatment of patients with cardiovascular comorbidity.

2.6.8.2. Adverse events

A large proportion (61-92%) of all patients reported an adverse event during treatment, regardless of treatment assignment. Overall, cardiac disorders, increased weight, and reproductive system and breast disorders occurred more frequently in the iloperidone group compared with the placebo group and active comparators.

Severe adverse events were overall reported in 15.6% of iloperidone-treated patients. In the placebo-controlled studies, severe adverse events were reported in 9.9% of iloperidone-treated patients, compared with 8.0% to 23.7% in the comparator groups. The main severe adverse events were psychiatric disorders. It is notable that there is clear reverse association with iloperidone dose, with the proportion experiencing psychiatric severe adverse events ranging from 4.0% (iloperidone 20-24 mg/d) to 14.0% (iloperidone 4-8 mg/d). The corresponding frequency in the placebo group was 7.0%. The pattern is less obvious when restricted to the placebo-controlled studies, but the numbers of patients and events are limited in that analysis.

Regarding adverse event after prolonged treatment, it seems as if the proportion occurring in the period >6–12 months is similar for iloperidone (44.4%), haloperidol (45.8%), and risperidone (44.4%). Comparisons with these active comparators should, however, be cautious since the dose of the active comparators appear higher than commonly used in current clinical praxis.

A coherent and clinically relevant discussion on which adverse events that have at least a reasonable possibility of a causal relationship with iloperidone has not been presented by the applicant and the proposed ADRs are not approvable.

2.6.8.3. Serious adverse event/deaths/other significant events

Serious adverse events

Serious adverse events were reported in 14.4% of iloperidone-treated patients. The corresponding event rate was 26 per 100 exposed PY. The event rate in the placebo group was 62 and ranged from 20-57 in the active comparator groups.

The occurrence rate of *serious psychiatric adverse events* is higher than placebo. It is unexpected that a substance indicated for treatment of schizophrenia has a similar or higher occurrence rate of *schizophrenia* as adverse event, when compared with placebo. The likely interpretation of these findings is low efficacy of iloperidone.

Serious tachycardia was reported in 0.1% of all iloperidone-treated patients. No case of serious tachycardia was reported in any other treatment groups.

There was no apparent imbalance in the occurrence of *suicidal ideation* and *suicide attempt*.

Deaths

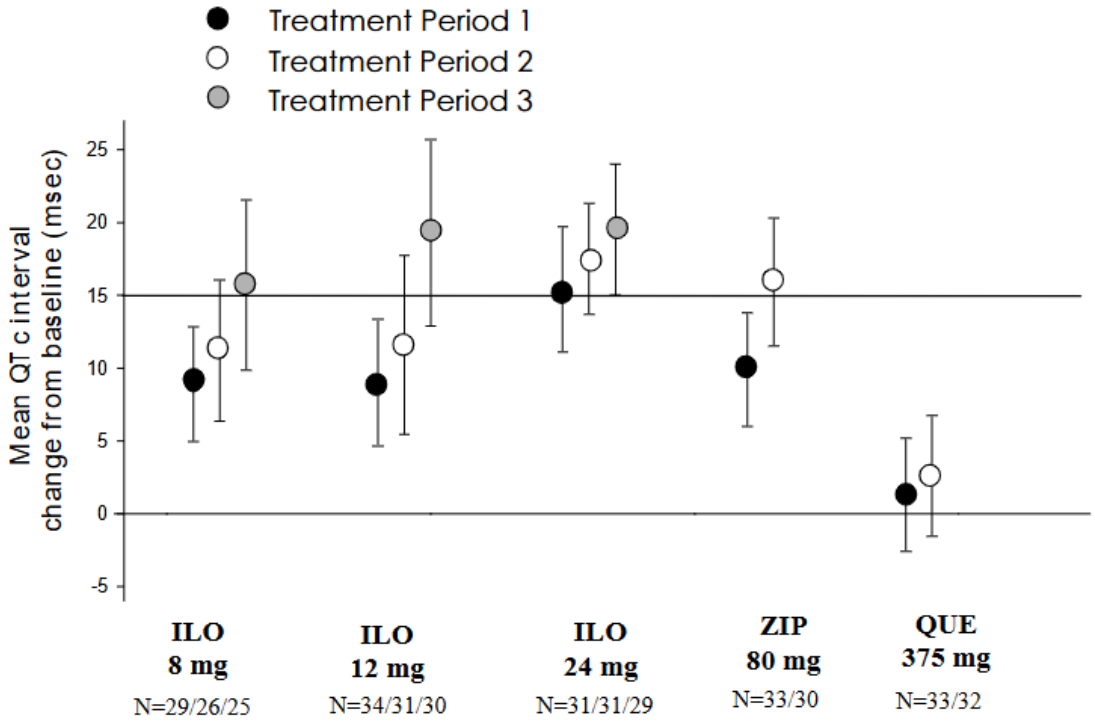
Overall, 27 patients died while participating in the iloperidone clinical development program. Seven (7) of these were patients not included in overall safety population. Most deaths occurred during the long-term double-blind or open-label treatment phases. Four (4) patients treated with iloperidone died of a cardiac event (sudden cardiac arrest or sudden death due to cardio-respiratory failure or cardiac failure) and two other patients treated with iloperidone died of "sudden death". There were no deaths from these causes in any of the comparison groups.

QT prolongation - TQT study

Of the 188 patients randomised, 149 (79%) completed the thorough QT (TQT) study. The study design is considered largely compliant with ICH E14. A drawback of the study design is that no placebo arm was included, and ECG-measurement were not conducted over a dosing interval, hampering an analysis of non-linearity or a delay between peak plasma concentration and QT-prolongation. Ziprasidone 80 BID was used as a positive control, which is an appropriate choice since it generally (alongside iloperidone) is considered one of the antipsychotics most likely to cause QT prolongation [1]. Quetiapine 375 mg BID was used as a negative control, and also this choice is appropriate. The QT interval was measured repeatedly 2-4 hours after administration of study drug, with the aim to measure at T_{max}.

The results from the TQT study support that iloperidone and P88 adversely affects the QT interval. The mean QTc changes from baseline at the expected t_{max} with iloperidone 8 mg BID and 12 mg BID were comparable to that of ziprasidone and followed similar patterns with the four different correction methods (Figure 16).

Figure 16: 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: * TMAX = estimated time of maximum concentration (ILO=2-4 hours post-dose; ZIP=5-7 hours post-dose; QUET= 1-2.5 hours post-dose)

During Treatment Period 2 (the presence of one metabolic inhibitor), the mean change from baseline in QTcF was highest in the iloperidone 24 mg q.d. (17.5+10.3 msec) and ziprasidone 80 mg BID (15.9+11.8 msec) groups, followed by the iloperidone 8 mg BID (11.2+12.0 msec) and iloperidone 12 mg BID (11.6+16.8 msec) groups.

During Treatment Period 3 (a second metabolic inhibitor added) the mean change in QTcF from baseline to steady state at T_{max} was highest in the iloperidone 24 mg QD (19.5+11.9) groups and iloperidone 12 mg BID (19.3+17.1), followed by the iloperidone 8 mg BID (15.7+14.1) group.

The comparisons of proportions with QTc increase ≥30 msec are varying depending on correction method used. The number and proportion of patients with QTcF increases of >30 msec from baseline to steady state at T_{max} during Treatment Period 1 was greatest in the iloperidone 24 mg QD [19/31 (61%)] group followed by the ziprasidone 80 mg BID [17/33 (52%], iloperidone 12 mg BID [15/34 (44%)], iloperidone 8 mg BID [9/29 (31%)], and quetiapine 375 mg BID [4/33 (12%)] groups, respectively.

Two patients in Treatment Period 1 and 2 experienced increases in QTcF of >60 msec from baseline to steady state at T_{max}. One patient was in the iloperidone 8 mg BID group and the other was in the iloperidone 24 mg QD group. No patients in any treatment arm had a QTcF value >500 msec.

The number and proportion of patients with QTcF increases of >30 msec from baseline to steady state at T_{max} during Treatment Period 3 was greatest in the iloperidone 12 mg BID [21/30 (70%)] and iloperidone 24 mg QD [20/29 (69%)] groups followed by the iloperidone 8 mg BID [13/25 (52%)] group.

QT prolongation - Dose dependence

Overall, there is a clinically relevant relationship between dose and QT prolongation. The mean increases in mean QT are of the same magnitude in the 8 mg BID and 12 mg BID iloperidone groups, and similar to the ziprasidone group. The proportion with QTc increase ≥30 msec suggests some relation with dose, comparing 8 mg BID vs. 12 mg BID. The 24 mg QD dose is consistently associated with a more adverse effect on the QT interval. While this dose is not in the recommended posology, it is in line with the ICH E14 guidance relevant to evaluate a wider dose range than the proposed.

QT prolongation - Relation to concentration

The average peak concentration of iloperidone clearly increased with increasing dose from 8 to 12 BID. However, as noted above the mean increases in QT were of the same magnitude but the proportion with QTc increase ≥30 msec increased. The statement by the Applicant that "*…plasma concentrations above ≈20 ng/mL do not appear to result in any further increase in the QTc interval*" is not agreed. In addition, the trend does not remain when both Iloperidone+P88 are accounted for (both shown to affect the hERG-channel at clinically relevant concentrations).

The concentrations measured in the TQT study were lower than those observed in patients. The C_{max} of iloperidone and P88 following 12 mg BID at steady state in patients is expected to be approximately 32 and 37 ng/ml respectively (dedicated dose-proportionality study *Study ILO5220112* with rich sampling). C_{max} of iloperidone and P88 in period 1 in the TQT study with 12 mg BID was only 21 and 24 ng/mL respectively. Furthermore, time-matched concentration-QTcF was only presented for measurements at 2 hours (not 4 hours, which is the expected T_{max} for the metabolite P88). These two important caveats regarding the available TQT study data raise further concerns that the risk may not be sufficiently characterised.

QT prolongation – Phase 3 studies

ECGs were performed in more than 85% of the overall safety population but may not have been taken at a time corresponding to C_{max}. The mean QTcF increased on average 5 msec through 3 months of treatment in the combined iloperidone group, compared with slight decreases at most time points in the placebo group. After Month 3, the mean change in QTcF in the iloperidone group gradually increased, reaching 15.0 msec from baseline in patients who received treatment for >12 months. The mean change in QTcF from baseline increased also in the haloperidol and risperidone groups, although not to the same extent as iloperidone at most time points. The level of impact on the QTcF was comparable to ziprasidone. When the evaluation was restricted to controlled study phases the difference in mean change in the QTcF interval was modest between iloperidone dose groups and similar to that for ziprasidone.

QT prolongation – Phase 3 outlier analyses

Overall, the proportions of patients who had a QTcF interval ≥450 msec were 3.8% in the iloperidone 10-16 mg/day group and 10.6% in the iloperidone 20-24 mg/day group, compared with 2.2% in the ziprasidone group and 1.1% in the haloperidol group. Stratified by sex the proportions were substantially higher in women, with 21.1% in the iloperidone 20-24 mg/day group exceeding a QTcF interval ≥450 msec. There were 16 patients (1.0%) exceeding a QTcF interval ≥450 msec in the combined iloperidone group, compared with no patient in the ziprasidone group.

In Study Group 1, three males and two females had a QTcF interval ≥500 msec using the Fridericia's formula. Three of these events occurred during the open-label treatment phase. Using the Bazett's formula, 32 patients in the combined iloperidone group had a QTcB interval ≥500 msec. No cases with QTc ≥500 msec were observed in any of the placebo or active comparator groups.

The percentage of patients in the combined iloperidone group (30.4%) who had an increase in QTcF interval of ≥30 msec was similar to that in the haloperidol group (31.5%), but higher than in the placebo (9.1%), risperidone (16.8%) and ziprasidone (23.1%) groups. This trend was observed in both males and females. There did not appear to be a dose-related increase in the percentage of patients who had an increase in QTcF interval of ≥30 msec in the 3 iloperidone dose groups.

The proportion with a ≥60 msec change of QTc in the overall safety population was 4.4% in the combined iloperidone group, compared with 1.6% in the ziprasidone group. In this comparison the relation to dose was somewhat inconsistent between the iloperidone dose groups, being highest (5.1%) in the 10-16 mg/day dose groups.

QT prolongation – Open label extension

In the open-label extension phase the mean maximum QTcF value was 413.21 msec, similar to that observed in the double-blind phase of the controlled studies. However, the mean change from baseline was slightly higher (+27.45 msec). In the overall safety population, three males and two females had a QTcF interval ≥500 msec. Three of these events occurred during the open-label treatment phase.

QT prolongation – Co-administered metabolic inhibitors and CYP2D6 polymorphisms

See section 2.6.8.

Heart rate

An increased heart rate is evident from the study results. In study group 2, the placebo-controlled trials, there were 30.1% in the iloperidone group that experienced a heart rate ≥120 bpm and an increase of ≥15 bpm, compare with 6.3% in the placebo group and ranging between 13.4-22.3% in the active comparator groups.

Blood pressure

The original presentation of study results on blood pressure in the application was based on outdated definitions of blood pressure limits [4]. Since iloperidone is intended for long-term treatment, the presentation of important safety data, such as categorisation of blood pressure, should be based on current clinical guidelines. While the Applicant acknowledges that current clinical consensus guidelines e.g. have lowered thresholds for blood pressure levels associated with increased cardiovascular risk, the Applicant elects to increase blood pressure cutoffs in definitions increased blood pressure. The previously used cutoff of 150 mmHg for systolic blood pressure has been increased to 180 mmHg instead of being lowered to 140 or 120 mmHg, which would have been appropriate according to the Guideline. For categorisation of low blood pressure, the cutoffs have been lowered. The presentation of data on blood pressure is consequently inappropriate and potentially misleading, despite of guidance to improve the presentation.

Considering that iloperidone has α1-aderenercic antagonist properties, hypotension is the blood pressure effect mainly in focus. In the placebo-controlled studies, a systolic blood pressure ≤90 mm Hg and a decrease of ≥10 mm Hg was seen in 18.2% in the iloperidone combined group, compared with 7.1% in the placebo group and ranging between 8.7-16.9% in active comparator groups. The relation with iloperidone dose was inverse, with highest proportion of 23.4% seen in the low-dose (4-8 mg/d) group. This may be a consequence of patients failing to tolerate an up-titration of the dose.

A similar pattern was seen for diastolic blood pressure, where a diastolic blood pressure ≤65 mm Hg and a decrease of ≥10 mm Hg was seen in 52.9% in the iloperidone combined group, compared with 34.9% in the placebo group and ranging between 30.2-44.9% in active comparator groups. The relation with iloperidone dose was also here inverse.

During open-label treatment (Study Group 4), 38.5% of patients had a diastolic blood pressure of ≤65 mm Hg and a decrease of ≥10 mm Hg. It is notable that blood pressure changes in the ILO-ILO group were similar to those in the PBO-ILO group, except for notable decreases in systolic blood pressure (ILO-ILO, 19.8%; PBO-ILO, 9.3%).

Orthostatic hypotension is of key interest since this is the reason for a dose titration procedure. Orthostatic hypotension was initially in the application defined as a drop in systolic blood pressure of greater than 30 mm Hg from supine to standing for 3 minutes. This is an outdated definition of orthostatic hypotension. A more contemporary consensus definition is that orthostatic hypotension is a sustained reduction of systolic blood pressure of at least 20 mmHg or diastolic blood pressure of 10 mmHg within 3 min of standing or head-up tilt to at least 60° on a tilt table [5]. With an updated contemporary definition, it is evident that iloperidone is associated with the highest incidence of orthostatic response, which was seen in 55.7% in the iloperidone combined group, compared with 36.5% in the placebo group and ranging between 36.2-56.8% in active comparator groups. The corresponding proportions with sustained orthostasis were 3.0% in the iloperidone combined group, compared with 0.1% in the placebo group and ranging between 0-1.7% in active comparator groups.

Hypotension and orthostatic blood pressure reactions are clearly associated with iloperidone, and the frequency of these events appear higher than active comparators and persist over prolonged treatment periods.

Cardiac adverse events

Cardiac AEs of mild or moderate severity occurred in 6.8% of patients in the combined iloperidone group in study group 1, which was higher than in any of the placebo (2.8%), haloperidol (2.9%), risperidone (1.9%), and ziprasidone (3.8%) groups. Serious cardiac AEs occurred in 0.4% both in the placebo and the iloperidone group.

Increased body weight

In the entire safety population, 30.5% of iloperidone-treated patients had a weight gain ≥7%, compared with 9.7% in the placebo group and ranging between 7.2-25.9% in active comparator groups. The increase was comparable across iloperidone dose levels.

During the open-label phase, the frequency of clinically relevant weight changes was slightly higher in patients continuing to receive iloperidone (35.0%) compared with those switching from placebo (29.1%). This suggests that this effect is not restricted to early phases of treatment.

Extrapyramidal Symptoms

The Applicant has elected to present results for extrapyramidal adverse effects only based on the Barnes Akathisia Scale (BAS), and not using the Extrapyramidal Symptoms Rating Scale (ESRS). The Barnes Akathisia Scale (BAS) comprises items for rating the observable, restless movements which characterise the condition, the subjective awareness of restlessness, and any distress associated with the akathisia. In addition, there is an item for rating global severity. Based on recorded BAS, regardless of BAS parameter, it is apparent that iloperidone causes slightly more akathisia compared to placebo but less compared to ziprasidone and risperidone and notably less than haloperidol.

It was noted that the ESRS showed a similar rating score in the iloperidone, risperidone and ziprasidone groups. It should be noted that while iloperidone appears to compare favourably to the other antipsychotics used as comparators in the clinical trials with regard to EPS and akathisia, the doses of the comparators were relatively high compared to today's clinical practice, albeit within the dose recommendations of the respective product information. The comparisons should therefore be interpreted with caution as they may have limited relevance considering current clinical practice.

2.6.8.4. Laboratory findings

Haematology

Laboratory data suggests that iloperidone, when compared to placebo, is associated with a higher frequences of low lymphocytes, monocytes, and platelets. In contrast to this, low white blood cells and low neutrophils occur at a similar frequency as in the placebo group. A warning was suggested for leukopenia, neutropenia and agranulocytosis. Patients with severe neutropenia should discontinue Iloperidone Vanda Pharmaceuticals. At the same time the suggested section 4.8 only mentions "*neutrophil count increased*" and "*white blood cell count*". The proposed SmPC did not reflect the actual study data submitted and the interpretation of safety data was inconsistent and contradictory.

Haematocrit

Lowered haematocrit appears substantiated and is described in the proposed ADRs section in product information. In Study 3201 (bipolar mania), iloperidone-treated patients experienced an average decrease of roughly 5% from baseline to Day 7, compared to an increase of 2% in placebo group.

Renal function

The increase in serum creatinine is concerning in the context of "haemodilution" stated in relation to reduced haematocrit. It should be noted that "haemodilution" is normally accompanied by lowered creatinine levels. A potential adverse impact on renal function is therefore a potential concern for long-term treatment.

Liver function analyses

Increases in ALT that seems to be mild and not associated with other changes in hepatic laboratory values were observed. "Alanine aminotransferase increased" was labelled as common in the proposed ADRs list. The single case that met Hy's law was likely related to cholelithiasis and cholecystitis.

Blood glucose

Iloperidone treated patients had a higher proportion of shifts from within normal range to higher than normal range of fasted glucose compared to placebo. There is, however, a striking discrepancy between the data currently presented on hyperglycaemia and the corresponding data previously submitted by the applicant. The applicant has clarified that the discrepancy is due to using several pooled terms related to "hyperglycaemia" in the previous application, while in the current application the result is presented for one specific term only. From a clinical perspective the former approach is more relevant. It does not make sense to separate "*hyperglycemia*" from "*blood glucose increased*". These terms reflect the same adverse pathophysiological impact. It is concluded that these results, as presented in the current application, should be viewed with caution, as they may not fully reflect the actual magnitude of adverse effects on blood glucose and glucose tolerance.

Blood lipids

There is a slight imbalance identified regarding lipid levels. Cholesterol outside the extended normal range (normal range +/-15%) was seen in 12.7% in iloperidone group and 10.6% in the placebo group. A post-baseline increase in cholesterol, from normal to outside the extended normal range, was seen in 10.8% in iloperidone treated and 9.9% in the placebo group. The change in LDL from baseline to worst value is slightly larger in the iloperidone group (0.75) compared to placebo (0.56). LDL over the extended normal range was seen in 9.2% in iloperidone treated and 11.0% in the placebo group. The corresponding proportions for triglycerides were 0.4% vs. 0.1%.

Prolactin

Iloperidone causes increased prolactin levels. This is mentioned in warnings but not in ADRs.

Serum Urate

The increase in uric acid is notable but there does not appear to be an increase in the proportion with high values, with 4.4% in the iloperidone group and 4.6% in the placebo group. A genetic predisposition has been identified by the applicant. but this is not mentioned in the ADRs. The potential adverse consequences of increased serum urate include increased cardiovascular risk during long-term treatment and in patients with other cardiovascular risk factors.

Electrolytes

An impact on electrolytes could be relevant for the risks associated with QTc prolongation. No such relevant impact has been observed.

2.6.8.5. In vitro biomarker test for patient selection for safety

Iloperidone is extensively metabolized. One major metabolite, P95, is formed via the CYP2D6 metabolic pathway. The applicant stated that the P95 metabolite does not appear to have pharmacologic effects on the central nervous system, but potential systemic effects are unclear. Effects of the P95 metabolite on the QT interval are unlikely with the concentrations seen with the proposed posology. CYP2D6 is an enzyme that is highly polymorphically expressed, and several genetic variants of functional relevance are known, which occurs in a notably high frequency in the European population. The exposure of the primary active metabolite P88, as well as exposure to the parent drug iloperidone, is increased in subjects who are poor CYP2D6 metabolisers and in subjects treated with CYP2D6 inhibitors, while the exposure of P95 is decreased. Exposure to P88 and iloperidone is also increased in case of co-administration with CYP3A4 inhibitors, and this effect is larger in subjects who are poor CYP2D6 metabolisers.

The randomized, open-label, parallel group, 2-cohort, 3-period crossover study IL0522 0104 characterized the pharmacokinetics of iloperidone in poor and extensive CYP2D6 metabolizers. The results of this study indicate that CYP2D6 polymorphisms influence iloperidone metabolism and higher concentrations of iloperidone are present in the plasma of poor CYP2D6 metabolizers.

Effect of co-administered metabolic inhibitors and CYP2D6 polymorphisms on the QTc Interval was evaluated in 128 of the patients included in the TQT study (2328). The results suggest that the *CYP2D6* genotype may be relevant to changes in QTc from baseline during treatment with iloperidone.

In study 3101 the CYP2D6*4 (1846GA or AA) or CYP2D6*10 (100CT or TT) polymorphisms were evaluated in a subset of patients. Treatment with iloperidone resulted in substantially higher mean changes in QTcF interval in the combined non-GG subgroups compared with the GG (wildtype) subgroup. No such impact of this polymorphism was seen following treatment with ziprasidone.

One objective of the whole genome association study conducted within study 3101 was to identify genetic markers associated with response to iloperidone in terms of the change from baseline of the QTcF interval at Day 14. The polymorphisms and new mutations in the CERKL gene associated with QT prolongation observed has not resulted in any meaningful attempt at risk minimisation but is a reminder that individual factors, including genetic susceptibility, will influence the risks associated with the adverse effects of iloperidone on the QTc interval.

The adverse effects of CYP2D6 polymorphism and CYP2D6 inhibitors on QTc prolongation is strong. The proposal therefore was that the target dose for CYP2D6 poor metabolisers and patients taking CYP2D6 or CYP3A4 inhibitors should not exceed 6 mg twice daily.

The applicant's strategy used for categorisation into different genotype groups in study IL0522 0104 is currently unclear. There is a risk that currently available data has underestimated the effects of CYP2D6 polymorphisms on iloperidone and P88 exposure.

Basing classification of metabolizer status only on the CYP2D6*4 and CYP2D6*10 polymorphisms is with current knowledge insufficient and associated with a substantial risk for misclassification. This also means that the available study data cannot provide sufficient characterisation of the impact on QTc prolongation from genetic polymorphism.

2.6.8.6. Safety in special populations

Older adults

There were only 23 patients 65 years or older in the study program for the indications applied for. 126 older adults were also included in two studies targeting elderly patients (60 to 90 years) with dementia (placebo-controlled study ILP3007 Part 1 and risperidone-controlled ILP3007 Part 2), where iloperidone doses were much lower than the posology currently applied for, and treatment periods were relatively short (ILP3007P1 one month, ILP3007P2 up to 3 months).In study ILP3007 Part 1 and Part 2 in iloperidone patients, cases of QT prolongation, postural hypotension, increased heart beats, chest pain, were reported as well as values above the upper limit of the extended normal range post-baseline for ALP, CPK, glucose, SGOT, SGPT, LDH, and for triglycerides, mean weight increase, dizziness, sedation, including falls (some with fractures, which were assessed not related to a study medication), and there were dose adjustments (due to sedation). Many of these adverse events were more frequently observed than in the placebo or risperidone arms.

Nevertheless, data from submitted short-term study ILP3007 Part 1 and ILP3007 Part 2 (different indications - treating psychotic and behavioral symptoms in elderly patients with dementia) do not allow proper analysis also because doses used were much lower (up to 48 times lower; ranging from 0.5 to 6 mg/day, while most of the doses were up to 2 mg/day) than doses recommended in the product information for indications of Iloperidone Vanda Pharmaceuticals (up to 24 mg/day).

A comparison provided for patients <50 years versus ≥50 years old did not suggest any obvious increase in AEs in patients ≥50 years old, however these include only few patients ≥65 years, making an analysis of older age groups inconclusive.

Considering the severe QT prolongation associated with iloperidone exposure, and the paucity of older patients exposed at a dose relevant for the indications applied for, extrapolation of safety to patients >65 years old is not appropriate.

Sex

There is no apparent difference between men and women in the proportion of patients experiencing adverse events. The Applicants modelling of pharmacokinetics suggests higher iloperidone exposure in females. While this modelling exercise is of questionable value, it is still of interest that no clear increased frequency of adverse events is seen in female patients.

Women are known to have longer QTc and be more sensitive to effects on the QTc. The proportions of patients who had a QTcF interval ≥450 msec in the pooled phase 3 data were substantially higher in women, with 21.1% in the iloperidone 20-24 mg/day group exceeding a QTcF interval ≥450 msec, compared to 6.0% in males.

Mild or moderate hepatic impairment

There is no relevant new safety information generated from the adverse events reporting from study ILO522A 0103.

Severe renal impairment

There is no relevant new safety information generated from the adverse events reporting from study ILO522 0102.

2.6.8.7. Safety related to drug-drug interactions and other interactions

Iloperidone is metabolised via several pathways, involving both CYP3A4 and CYP2D6. The effects of strong inhibitors of CYP3A4 and CYP2D6 on the exposure of iloperidone and metabolites have been investigated in vivo in healthy subjects (see the Clinical Pharmacology section for further details).

In summary, the strong CYP3A4 inhibitor ketoconazole (Study 0107) increased AUC and Cmax of both iloperidone and P88 in CYP2D6 extensive metabolisers about 1.6-fold. The increase in exposure for P95 was somewhat lower (1.4-fold). The strong CYP2D6 inhibitor fluoxetine (Study 0108) increased iloperidone exposure (AUC) 2.4-fold and P88 2.2-fold, while C_{max} increased about 1.7-fold for both substances. Data on the effects of concomitant inhibition of CYP3A4 and CYP2D6 is available from the thorough QT study (Study 2328) in patients with schizophrenia or schizoaffective disorder, but only the effects on C_{max} were determined. The strong CYP2D6 inhibitor paroxetine resulted in 1.6-1.7-fold increases in C_{max} for both iloperidone and P88 and with combined administration of paroxetine and ketoconazole, there was a 2.3-fold increase in in C_{max} for iloperidone and a 2.3-2.7-fold increase for P88 compared to administration without inhibitors.

There was a recommendation to reduce the (maximum) dose by 50 % with concomitant administration of a strong CYP3A4 or a strong CYP2D6 inhibitor or with combined use of both inhibitors. It has not been demonstrated that the proposed dose adjustment would result in safe concentrations in case of combined use of both a strong CYP3A4 and a strong CYP2D6 inhibitor, or in patients who are CYP2D6 poor metabolisers (PMs) treated with a strong CYP3A4 inhibitor.

There is also a recommendation to reduce the maximum dose by 50% in (known) CYP2D6 PMs but there was currently no requirement stipulated that patients should be genotyped before starting treatment with iloperidone and thus it would not always be known if patients are CYP2D6 PMs or not.

In addition, there are no clinical data with less potent CYP2D6 or CYP3A4 inhibitors. A warning statement was proposed but the proposed monitoring is not considered feasible and amendment is needed.

These are considered critical issues for the safety of iloperidone, especially considering the risk for QT prolongation.

Overall, it has not been sufficiently justified that the currently proposed dose adjustments in case of concomitant interacting drugs are adequate and will result in safe concentrations for the broad target population(s).

2.6.8.8. Discontinuation due to adverse events

AEs led to dose modification in 14.6% of iloperidone-treated patients, which was a higher proportion than in the placebo group (3.1%), the ziprasidone group (3.3%), and the risperidone group (10.0%), but lower than the proportion for haloperidol (20.5%).

Dose modification due to psychiatric disorders was seen among 5.9% in the iloperidone group and 1.6% in the placebo group. Restricting the comparison to placebo-controlled studies (study group 2),

these proportions were comparable between iloperidone and placebo. The proportion of such events would be expected to be higher in the placebo group and indicates suboptimal efficacy of iloperidone.

While the frequency of permanent discontinuation overall for iloperidone was comparable with the other active comparator groups, it was higher compared with placebo (10.0% vs. 4.6%). Looking at specific SOCs, no clear pattern is evident when comparing the different treatment groups.

2.6.8.9. Post marketing experience

The product has been marketed for 15 years in the US. Post marketing experience would therefore be expected to be important, particularly concerning QT prolongation and the associated risk for TdP and sudden cardiac death. The submitted data unfortunately did not provide such relevant information.

The table referred to by the applicant provided counts of adverse reactions by system organ class (SOC) for all events reported to the post-marketing safety surveillance database. This provided no relevant information.

The periodic safety update reports are provided without any overall summary and discussion. They provide no relevant information.

It is important to acknowledge that a characterisation and quantification of the risks associated with QT prolongation require systematic study in a setting where sudden deaths can be reliably captured. This is a well-known limitation of non-interventional studies in the US. No attempt to study this important safety concern post marketing is reported.

In general, spontaneous reporting of suspected adverse reactions can only generate safety signals and are not expected to provide meaningful information to estimate incidence of clinically relevant QT prolongation and associated risk for cardiovascular death. This is a particular concern since the target population is expected to have an increased risk for sudden death also from other causes.

There is consequently no meaningful and reassuring data from the post marketing period in the USA.

2.6.9. Discussion on clinical safety

The integrated safety database in the current application consists of 4852 patients exposed to iloperidone in 12 of a total of 40 clinical studies. The rationale for restricting the safety database to 12/40 studies has been discussed. A review of ECG data, which are of key interest for characterising the safety of iloperidone, from non-pooled studies, did not increase the safety concern. But since the applicant has elected to not comprehensively review these data in the submission, this does not contribute with any reassurance. The issue is not further pursued.

Iloperidone is intended for long-term treatment at least in the schizophrenia indication. Only 171 patients received the highest daily dose of 20-24 mg for >6 months and only 80 patients for >12 months. The number of patients exposed long-term to the highest dose in controlled clinical trial setting is consequently low.

Exclusion of patients with preexisting cardiovascular disease and mandatory prolonged hospitalisation in the clinical trial setting questions if important parts of the safety characterisation can be extrapolated to clinical practice. The key study 3101 required patients to be hospitalised for 4 weeks during treatment initiation. These restrictions of the study population were not reflected in the proposed product information.

The product has been marketed for 15 years in the USA but the submission does not include any systematic post marketing study. The key safety concern regarding QT prolongation and the associated

risk for TdP and sudden cardiac death has therefore not been further studied during more widespread use in clinical practice. It is important to acknowledge that a characterisation and quantification of the risks associated with QT prolongation require systematic study in a setting where sudden deaths can be reliably captured. This is a well-known limitation of non-interventional studies in the USA. No attempt to study this important safety concern post marketing is reported.

In general, spontaneous reporting of suspected adverse reactions can only generate safety signals and are not expected to provide meaningful information to estimate incidence of clinically relevant QT prolongation and associated risk for cardiovascular death. This is a particular concern since the target population is expected to have an increased risk for sudden death also from other causes. There is consequently no meaningful and reassuring data from the post marketing period in the USA.

The proposed indication specifies adults as the target population, therefore including older patients without age restriction. Considering that only very few patients >65 years old were included in the study, and the serious concern raised not only regarding QT prolongation, but also other cardiovascular risk factors, the lack of any safety characterisation using the proposed posology in older patients is a concern.

Adverse reactions

While the overall safety profile largely corresponds to what would be expected from a substance in this class, the prolongation of the QT interval, in combination with a highly complex metabolism related to genetic factors, raises serious concerns. Adverse events after prolonged treatment occur with a frequency comparable to haloperidol and risperidone.

The main severe adverse events observed were psychiatric disorders. It is notable that there is reverse association with iloperidone dose. The occurrence rate of *serious psychiatric adverse events* is comparable to the placebo group in the overall safety population and higher than placebo in the placebo-controlled studies. It is unexpected that a substance indicated for treatment of schizophrenia has a similar or higher occurrence rate of *schizophrenia* as adverse event, when compared with placebo. The likely interpretation is that these findings are related to low efficacy of iloperidone.

A major concern with the application is that the applicant has failed to provide relevant justification for the ADRs. The source for adverse events to be considered as potential adverse reactions is the tabulated summary of pooled frequencies of TEAEs with any relatedness to iloperidone treatment in the combined group iloperidone group which are equal to or greater than placebo in study Group 2. This pool consists of 1550 patients treated with iloperidone (all doses combined) and 795 patients treated with placebo, representing all patients enrolled in double-blind placebo-controlled studies 3000, 3004, 3005, 3101 and 3201. The selection of this pool as a basis for identifying adverse reactions is acceptable. The serious problem with this strategy is that no threshold for the frequency of occurrence of each adverse event has been used. This means that there is no mechanism to deal with minor unbalance due to chance (random error) for non-serious events with no known biological plausibility. Multiple entries are based on a single occurrence in the iloperidone group and without any further justification.

There are also important adverse reactions identified from the Summary of Clinical Safety, that are not included as ADRs. Important risk minimisation measures, clearly relevant considering the safety concerns identified have not been implemented in the proposed product information.

QTc interval prolongation

The design of the TQT study is considered largely compliant with ICH E14. Unfortunately, no placebo arm was included, and ECG-measurement were not conducted over a dosing interval, hampering an analysis of non-linearity or a delay between peak plasma concentration and QT-prolongation.

Ziprasidone 80 BID was used as a positive control, which is an appropriate choice since it generally (alongside iloperidone) is considered one of the antipsychotics most likely to cause QT prolongation.

The results from the TQT study support that iloperidone and the active metabolite P88 adversely affects the QT interval to a degree at least comparable to that of ziprasidone. The study may not have captured the full extent of adverse impact on the QT interval. Women had a stronger effect on the QT interval and were also underrepresented (30%) in the TQT study. This is a limitation and raises concern since women are expected to have longer QT and also be more sensitive to QT prolongation [2]. The clearly higher impact in women is not unexpected, but no risk minimisation based on sex is proposed by the applicant.

It is important to note that the C_{max} of iloperidone and P88 following 12 mg BID at steady state in patients is expected to be approximately 32 and 37 ng/ml respectively (dedicated dose-proportionality study *Study ILO5220112* with rich sampling). C_{max} of iloperidone and P88 in period 1 in the TQT study with 12 mg BID was only 21 and 24 ng/mL respectively. Time-matched concentration-QTcF was furthermore only presented for measurements at 2 hours and not 4 hours (including all treatment periods), which is the expected T_{max} for the active metabolite P88. These two important caveats regarding the available data raise further concerns that the risk may not be sufficiently characterized.

Data on QTc interval from the phase 3 studies should be interpreted with some caution since ECGs may not have been taken at a time corresponding to C_{max}. The magnitude of impact was still at least of a similar magnitude as for ziprasidone. Outliner analyses rather support a stronger impact of iloperidone on severe prolongation of QTc.

An important observation is that the mean QTcF change from baseline continued to increase beyond 12 months of treatment. The problem is consequently not restricted to the treatment initiation phase. This is further supported by the observation that 3/5 events with a QTcF interval ≥500 msec occurred during the open-label treatment phase. This is notable, since it illustrates that evaluation of QT at treatment initiation does not provide sufficient risk minimisation. Risk minimisation strategies must be implemented and effective over prolonged treatment periods. No such sufficient strategies have been identified.

Iloperidone dose (within therapeutic range) did not appear to be clearly predictive of clinically relevant QTc prolongation. While the risk for QTc prolongation is related to concentration, this still raises a concern for the effectiveness of reduced iloperidone dose as a risk minimisation measure.

Deaths

The ultimate adverse consequence of QTc prolongation is ventricular arrhythmias (*torsade de pointes*) and cardiac arrest. Four (4) patients treated with iloperidone died of a cardiac event and two more patients treated with iloperidone died of "sudden death". There were no deaths from these causes in any of the comparison groups. Acknowledging the low number of deaths, this still suggests an adverse effect of iloperidone on mortality, potentially reflecting the adverse effects on the QTc interval. This imbalance is seen even though there are few patients exposed >12 months in the safety database. The mortality risk associated with QTc prolongation is expected to be strongly related to interaction with other risk factors, that may develop during prolonged treatment. As noted above, patients with cardiovascular conditions were excluded from the study populations but are not excluded from the proposed target populations.

A potential adverse effect on the risk for t*orsade de pointes* and sudden cardiac death, caused by iloperidones established pronounced adverse effects on the QT interval, is supported by the data in the development program, but the magnitude of this serious concern remains insufficiently characterised. Long-term exposure in the development program is insufficient for this purpose and no relevant post-marketing study data has been submitted.

Other important safety concerns – long-term cardiovascular safety not related to QTc

Hypotension and orthostatic reactions are prominent, requiring a slow up-titration of the dose. When categorising blood pressure to describe the magnitude of this problem, the data was initially presented based on an outdated definition of orthostatic hypotension. The results presented were therefore an underestimation of the proportion of patients affected by this adverse reaction. There is a remaining high proportion with hypotension also during the open-label extension phase, even in patient continuing treatment with iloperidone from the controlled phase. This suggests that hypotension continues to be a problem also during prolonged treatment and is not restricted to the titration phase.

An *increased heart rate* from iloperidone exposure is evident but has not been acknowledged by the Applicant from the perspective of being one more cardiovascular risk factor during prolonged treatment with iloperidone and in relation to patients with cardiovascular comorbidity.

Weight gain and *lowered haematocrit* were consistently observed and by the Applicant attributed to fluid volume changes. About 1/3 of iloperidone-treated patients experienced a weight gain of ≥7% from baseline. The Applicants discussion on the mechanism behind these effects is not agreed. If it is related to body water, then it means that iloperidone causes fluid retention. Fluid retention must be based on increased intake and/or failure to excrete water normally. It cannot merely be a consequence of fluid shift between compartments. The observed *increase in serum creatinine* also raises further concern in this context. It should be noted that "haemodilution" is normally accompanied by lowered creatinine levels. Long-standing fluid retention should be considered potentially associated with long-term cardiovascular risk and the Applicant has failed to acknowledge this concern in relation to cardiovascular safety.

Further concerns related to long-term cardiovascular safety are *increased lipid levels* and *increased uric acid levels*, factors that during long-term treatment are to be considered cardiovascular risk factors.

Extrapyramidal symptoms

The Applicant has elected to present results for extrapyramidal adverse effects only based on the Barnes Akathisia Scale (BAS), and not using the Extrapyramidal Symptoms Rating Scale (ESRS). It was noted that the ESRS showed a similar rating score in the iloperidone, risperidone and ziprasidone groups. It should be noted that while iloperidone appears to compare favourably to the other antipsychotics used as comparators with regard to extrapyramidal symptoms and akathisia, the doses of the comparators were relatively high compared to today's clinical practice, albeit within the dose recommendations of their respective SmPC. The comparisons should therefore be interpreted with caution as they may have a limited current clinical relevance.

2.6.10. Conclusions on the clinical safety

The characterisation of safety mainly rests on exposure shorter than 6 months, and mandated hospitalisation, exclusion of all patients with prevalent cardiovascular disease, and failure to include older adults. The safety profile is dominated by psychiatric adverse events, casting doubt over the efficacy of iloperidone, and severe prolongation of the QTc interval. The magnitude of this latter adverse effect is at least as severe as from ziprasidone, likely more severe. An increased risk for QT prolongation is present throughout the observed follow-up. The ultimate concern is an increased risk for life-threatening arrythmias and sudden death. In the study program six patients treated with iloperidone died of a cardiac event or in a "sudden death". There were no deaths from these causes in any of the comparison groups. This occurred despite restricting inclusion of patients with

cardiovascular conditions in the trials. Important aspects of this adverse effect of iloperidone remain uncharacterised.

The risks associated with QT prolongation are further aggravated by the extensive metabolism of iloperidone with a strong impact of genetic polymorphisms that would mandate genetic profiling of all patients. It is strongly questioned that feasible and effective risk minimisation can be achieved. The Applicant has failed to acknowledge a number of safety concerns with a potentially important impact on long-term cardiovascular safety. Unfortunately, no post marketing safety study has been conducted in the USA.

In summary, the adverse safety profile of iloperidone that has been identified, together with concerns for long-term cardiovascular safety in clinical practice, and insufficient risk minimisation that fails to address the relevant safety concerns. These safety concerns have a substantial negative impact on the benefit/risk balance.

2.7. Risk Management Plan

The CHMP, having considered the data submitted in the application was of the opinion that due to the concerns identified with this application, the risk management plan cannot be agreed at this stage.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP and PRAC, having considered the data submitted by the applicant, were of the opinion that, due to the concerns identified with this application, as above outlined, the pharmacovigilance system summary cannot be agreed at this stage.

2.8.2. Periodic Safety Update Reports submission requirements

Not applicable.

2.9. Product information

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

2.9.1. 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.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The proposed indication for iloperidone is:

- Treatment of schizophrenia in adults.
- Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults.

A common aim of therapy in both conditions is to shorten the duration of a psychotic or manic/mixed episode. In schizophrenia another aim is to reduce the risk of relapse which implies a potentially very long duration of treatment as the risk of relapse remains throughout life.

The applicant has not applied for maintenance treatment for bipolar disorder.

3.1.2. Available therapies and unmet medical need

For the treatment of schizophrenia, antipsychotic agents (dopamine receptor antagonists/partial agonists) are the standard of care, preferably combined with non-pharmacological treatment approaches. For the acute treatment of manic or mixed episodes, lithium, antipsychotics and mood stabilisers can be used.

There are several approved medicinal products for both conditions, and although national, European and other treatment guidelines exist, the treatment choice is largely left to the discretion of the individual prescriber. For schizophrenia, one of the newer "second generation" or "atypical" antipsychotics is usually recommended for first-episode patients, and clozapine is recommended for patients who have had an inadequate response to at least two other antipsychotic medications.

Although many treatment options exist, there is an unmet medical need as treatment discontinuation is very common in both schizophrenia and bipolar disorder, because of actual or perceived lack of effect, side effects, limited patient understanding of their condition, and the risk of relapse.

3.1.3. Main clinical studies

The evidence of the efficacy of iloperidone in the treatment of schizophrenia is mainly based on data from four prospective, randomized, double-blind, placebo- and active-controlled, multicentre short-term studies (3000, 3004, 3005, 3101) and one randomised withdrawal study (2301). The short-term studies included patients with schizophrenia or schizoaffective disorder with at least moderately severe psychotic symptoms. The randomised withdrawal study included patients with schizophrenia who were not severely ill or worse, and whose treatment was associated with an insufficient efficacy and/or tolerability/safety concerns warranting a change of treatment.

The evidence of the efficacy of iloperidone in the treatment of acute manic or mixed episodes associated with bipolar I disorder in adults is based on data from a single phase III prospective, randomized, double-blind, placebo-controlled, multicentre short-term study. It included patients with bipolar I disorder with an ongoing manic or mixed episode of at least moderate severity, who were voluntarily hospitalised.

The characterisation of safety is based on four sets of study pools generated from the 12 integrated, Phase 2/3 clinical studies as follows (Table 39):

- **Study Group 1** – Therapeutic studies of patients with any iloperidone exposure: all patients enrolled into studies in all phases (controlled and uncontrolled) of all 12 studies combined (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);
- **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 five placebo-controlled studies combined;
- **Study Group 3** – Therapeutic studies of patients with any double-blind placebo-controlled or active-controlled study phase iloperidone exposure (excluding any exposure during open label extension phase);
- **Study Group 4** – Open-label iloperidone exposure: patients who received iloperidone in the open-label extension phase of any of the 11 studies.

Table 39: Analysis groupings for the twelve integrated clinical studies in the safety database

Study Groups						
Study ID	Group		Group 1	Group 2	Group 3	Group 4
	Group Type		Any iloperidone exposure	Placebo-controlled studies only	Active-controlled including placebo	Open label extensions only
	Analysis Period		All periods (full ISS pooled safety population)	Double-blind periods of 4-week and 6-week studies	Double-blind periods ranging from 28 days to 12 months	Up to 12 months
	Phase	Study type				
2001	2b	Safety	✓		✓	✓
2328 [a]	2a	TQT	✓			
3000	3	Efficacy	✓	✓	✓	✓
3001	3	Efficacy	✓		✓	✓
3002	3	Efficacy	✓		✓	✓
3003	3	Efficacy	✓		✓	✓
3004	3	Efficacy	✓	✓	✓	✓
3005	3	Efficacy	✓	✓	✓	✓
3101 [b]	3	Efficacy	✓	✓	✓	✓
D2301 [b]	3	Efficacy	✓		✓	✓
US01	4	Switching	✓			✓
3201 [b]	3	Efficacy	✓	✓	✓	✓

Studies are presented in descending order by year completed (e.g., Study VP-VYV-683-3201 was the most recent study completed in patients with bipolar mania). All studies enrolled psychiatric patients with diagnoses of schizophrenia, schizophrenia and schizoaffective disorder, or bipolar I disorder. All efficacy studies also evaluated safety. TQT=thorough QT study.
[a] For TQT Study 2328, only period 1 (without metabolic inhibitors) is included the pooled safety analyses.
[b] Phase 3 studies completed by Vanda; all other studies shown were conducted by Novartis.

3.2. Favourable effects

3.2.1. Schizophrenia

Of the 4 short-term trials in schizophrenia, 2 trials had primary results that were statistically significant (studies 3004 and 3101), and 2 trials did not (3000 and 3005). In study **3004**, the mean difference in change from baseline to week 6 in the 18-item PANSS-derived BPRS (range 18-126) between the

iloperidone 10-16 mg group and the placebo group was 4.9, which was statistically significant (p=0.001). However, there were a lot of missing data, so the applicant was asked to conduct a sensitivity analysis with jump-to-reference multiple imputation. Using this method, the point estimate decreased from 4.9 to 2.99, and the effect was no longer statistically significant (p=0.0696), so the primary efficacy results of study 3004 were considered non-robust.

In study **3101**, the mean difference in change from baseline to week 4 in PANSS total score (range 30-210) between the iloperidone group and the placebo group was -4.92, which was statistically significant (p<0.01). There were a lot of missing data in this study as well, so the applicant was asked to conduct a sensitivity analysis with jump-to-reference multiple imputation. In this sensitivity analysis, the point estimate decreased from -4.92 to -3.05, and the difference was no longer statistically significant (p=0.09), so the primary efficacy results of study 3101 were considered non-robust.

In the initially presented results from the randomised withdrawal study **2301** the relapse rate was lower in the iloperidone group (20.4%, 95% CI 12.9 - 31.4) compared to the placebo group (63.4%, 95% CI 52.7 - 74.1). The mean time to relapse was 139 days in the iloperidone group compared to 71 days in the placebo group. The estimated hazard ratio (95% CI) was 4.7 (2.7, 8.3). In the additional sensitivity analysis in all randomised patents with baseline data, counting premature trial discontinuation as an event, the mean time to relapse was 125 days in the iloperidone group compared to 78 days in the placebo group (p<0.0001) and the relapse rate (95% CI) was 63.4% (55.8 - 71.0) vs 87.4% (81.5 - 92.1). The estimated hazard ratio (95% CI) was 1.9 (1.5 - 2.5). The secondary endpoint changes in PANSS-T score and CGI measures, all linked to the definition of relapse, were in favour of iloperidone treatment over placebo. The adjusted mean change (SD) in PANSS score was 1.2 (10.09) in the iloperidone group vs 13.3 (15.20) in the placebo group, nominal p-value <0.0001. The percentage of patients with a global improvement rating on the CGI-I of 4 (i.e., no change) at the last visit of the DBRP phase was significantly higher in the iloperidone treatment group (30.7%) compared with the placebo treatment group (20.3%; nominal p <0.0001).

3.2.2. Bipolar disorder, acute mania or mixed episode

In the single short-term study 3201, the primary endpoint (the change from baseline to week 4 in YMRS total score) was met. In the primary analysis, the mean difference in change between the iloperidone group and the placebo group was -4.0 points (95% CI -5.70, -2-25), p-value 0.000008. The applicant was asked to conduct a sensitivity analysis with jump-to-reference multiple imputation after which the average reduction compared to placebo was 3.2 points (95% CI not presented by the applicant), p<0.0001.

Several secondary endpoints were evaluated. For change from baseline in YMRS total score at each visit, the iloperidone treatment groups separated from the placebo group with nominal statistical significance at day 14. The reduction compared to placebo was -1.4 points. YMRS response was defined as the percentage of patients who achieved ≥50% reduction in YMRS Total Score. At week 4, this was achieved for 43.4% of patients in the iloperidone group and 33.5% of patients in the placebo group, nominal p-value 0.0248.

A nominally significantly greater reduction (improvement) from baseline in CGI-S was demonstrated by the iloperidone group compared with placebo at Day 21 (-1.2 and -0.9, respectively, p=0.0146) and at study endpoint (-1.5 and -1.1 for iloperidone and placebo, respectively, at Day 28, p=0.0005).

The change in depressive symptoms from baseline to week 4, as measured with the MADRS showed no nominally significant difference between iloperidone and placebo, with a mean reduction of 2.7 and 1.8 points in the iloperidone and placebo groups, respectively.

3.3. Uncertainties and limitations about favourable effects

3.3.1. Schizophrenia

Although iloperidone increased the time to relapse/impending relapse in Study 2301, the short-term efficacy of iloperidone in the treatment of schizophrenia has not been robustly demonstrated. Only 2 out of the 4 short-term trials in schizophrenia showed a statistically significant effect in the primary analysis, and these results were no longer statistically significant when missing data were handled using a reasonably conservative imputation method (jump-to-reference).

According to literature, the magnitude of the effect in all short-term studies falls below the minimum clinically important difference (MCID)[1] for the assessment instrument used[2]. In addition, there were numerical differences with respect to the magnitude of the effect and the time to onset of effect not favouring iloperidone in comparison to the active comparators (risperidone and haloperidol) included in the pivotal studies.

3.3.2. Bipolar disorder, acute mania or mixed episode

The magnitude of the effect of iloperidone treatment compared to placebo was modest in the primary analysis and decreased in the additional sensitivity analysis**.** The MCID for YMRS has been estimated to approximately an absolute decrease of 4 to 8 YMRS points or a 21% to 29% reduction of YMRS baseline score[3]. In a previous study using YMRS and CGI scores from a cohort of patients with acute manic/mixed state of bipolar disorders (N=3459), the YMRS minimal clinically relevant difference was 6.6 points. In another study linking YMRS and CGI scores based on individual-level participant data from eight double-blind, randomised placebo clinical trials on mania, a reduction of CGI-S by one point as well as 'minimally improved' on the CGI-I corresponded approximately to an absolute decrease of 4 to 8 YMRS points or a 21% to 29% reduction of YMRS baseline score whereas a reduction of CGI-S by two points and 'much improved' on the CGI-I corresponded to an absolute decrease of 10 to 15 points or a 42% to 53% reduction of YMRS baseline score

Further, there are concerns about a delayed onset of effect of iloperidone potentially due to the need for slow up titration of the dose. Just as in schizophrenia, the acute mania or mixed episode of a bipolar disorder can be associated with intense suffering for the patient and the risks of a wide range of adverse outcomes including aggression towards self and others is increased, making time to onset an important component of treatment efficacy. Further, there was no evaluation of maintenance of effect past four weeks with an active control, rendering this important aspect of acute treatment insufficiently characterised. There were, however, no indications that iloperidone treatment caused a switch from a manic or mixed state to a depressive state during the short-term study.

[1] Defined as "the smallest difference in a score in the domain of interest which patients [or providers] perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a meaningful change in the patient's management." *Jaeschke, R., et al. (1989)*. "Measurement of health status. Ascertaining the minimal clinically important difference." Control Clin Trials 10(4): 407-415.

[2] **PANSS**: between a 19% and 34% change in PANSS total score; *Hermes, E. D., et al. (2012).* "Minimum clinically important difference in the Positive and Negative Syndrome Scale with data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)." J Clin Psychiatry 73(4): 526-532. **BPRS**: a percentage reduction of the BPRS by approximately 28 percentage points reflected a reduction of the CGI severity score by one severity step, and a 10-points reduction corresponded roughly to minimal improvement. *Leucht, S., et al. (2006).* "Linking the PANSS, BPRS, and CGI: clinical implications." Neuropsychopharmacology 31(10): 2318-2325.

[3] *Lukasiewicz, M., et al. (2013)*. "Young Mania Rating Scale: how to interpret the numbers? Determination of a severity threshold and of the minimal clinically significant difference in the EMBLEM cohort." Int J Methods Psychiatr Res 22(1): 46-58. *Samara, M. T., et al. (2023)*. "Linkage of Young Mania Rating Scale to Clinical Global Impression Scale to Enhance Utility in Clinical Practice and Research Trials." Pharmacopsychiatry **56**(1): 18-24.

3.4. Unfavourable effects

Severe adverse events were overall reported in 15.6% of iloperidone-treated patients. In the placebo-controlled studies, severe adverse events were reported in 9.9% of iloperidone-treated patients, compared with 8.0% to 23.7% in the comparator groups. Regarding adverse event after prolonged treatment, it seems as if the proportion occurring in the period >6–12 months is similar for iloperidone (44.4%), haloperidol (45.8%), and risperidone (44.4%). Comparisons with these active comparators should, however, be cautious since the dose of the active comparators appear higher than commonly used in current clinical praxis.

Psychiatric adverse effects – lack of efficacy

The main severe adverse events observed were psychiatric disorders. The occurrence rate of *serious psychiatric adverse events* in the overall safety population was 11.2% in the combined iloperidone group and 4.4% in the placebo group. There is a reverse association with iloperidone dose, with the proportion experiencing psychiatric severe adverse events ranging from 4.4% (20-24 mg/d) to 13.6% (4-8 mg/d). It is unexpected that a substance indicated for treatment of schizophrenia has a similar or higher occurrence rate of *schizophrenia* as adverse event, when compared with placebo. The likely interpretation is that these findings are related to low efficacy of iloperidone.

QTc prolongation

The concerns regarding the safety profile are otherwise primarily focused on the effects of iloperidone on the QTc interval. Both the results from the TQT study and integrated phase 3 data indicate that iloperidone and its active metabolite P88 adversely affects the QT interval to a degree at least comparable to that of ziprasidone, which is considered to be one the antipsychotics with strongest effect on the QTc. Since women had a notably stronger effect on the QTc and were underrepresented in the studies, the average effects reported may to some extent be misleading.

The results from the TQT study support that iloperidone and P88 prolongs the QT interval to a degree at least comparable to ziprasidone. The mean QTc changes from baseline at the expected t_{max} with iloperidone 8 mg BID (ΔQTcF 8.9±10.5) and 12 mg BID (ΔQTcF 9.0±12.5) were comparable to that of ziprasidone 80 mg BID (ΔQTcF 9.9±11.0) and followed largely similar patterns with the four different correction methods. The comparisons of proportions with QTc increase ≥30 msec are varying depending on correction method used. The applicant has not provided a justification for which correction method to prefer. The number and proportion of patients with QTcF increases of >30 msec from baseline to steady state at t_{max} during Treatment Period 1 was greatest in the iloperidone 24 mg q.d. [19/31 (61%)] group followed by the ziprasidone 80 mg b.i.d. [17/33 (52%], iloperidone 12 mg b.i.d. [15/34 (44%)], iloperidone 8 mg b.i.d. [9/29 (31%)], and quetiapine 375 mg b.i.d. [4/33 (12%)] groups, respectively. There were single occurrences of QTc increase ≥60 msec in all iloperidone groups but no such event seen in the ziprasidone group. No patients in any treatment arm had a QTcF value >500 msec.

Overall, the proportions of patients who had a QTcF interval ≥450 msec in phase 3 studies were 3.8% in the iloperidone 10-16 mg/day group and 10.6% in the iloperidone 20-24 mg/day group, compared with 2.2% in the ziprasidone group and 1.1% in the haloperidol group. Stratified by sex the proportions were substantially higher in women, with 21.1% in the iloperidone 20-24 mg/day group exceeding a QTcF interval ≥450 msec. There were 16 patients (1.0%) exceeding a QTcF interval ≥450 msec in the combined iloperidone group, compared with no patient in the ziprasidone group. A few patients in the 10-16 and 20-24 mg/day iloperidone groups also had a QTcF interval ≥500 msec, compared with no patient in the active comparator groups.

The percentage of patients in the combined iloperidone group (30.4%) who had an increase in QTcF interval of ≥30 msec was similar to the incidence in the haloperidol (31.5%), but higher than in the placebo (9.1%), risperidone (16.8%) and ziprasidone (23.1%) groups. This trend was observed in both males and females. There did not appear to be a dose-related increase in the percentage of patients who had an increase in QTcF interval of ≥30 msec among the 3 iloperidone dose groups.

The proportion with a ≥60 msec change of QTc from baseline in the overall safety population was 4.4% in the combined iloperidone group, compared with 1.6% in the ziprasidone group. In this comparison the relation to dose was somewhat inconsistent between the iloperidone dose groups, being highest (5.1%) in the 10-16 mg/day dose groups.

The effects on the QTc interval are not restricted to the treatment initiation phase. The mean QTcF change from baseline continued to increase beyond 12 months of treatment and 3/5 events with a QTcF interval ≥500 msec occurred during the open-label treatment phase.

A potential adverse effect on the risk for t*orsade de pointes* and sudden cardiac death, caused by iloperidones established pronounced adverse effects on the QT interval, is supported by the data in the development program, but the magnitude of this serious concern remains insufficiently characterised. In the study program six patients treated with iloperidone died of a cardiac event or in a "sudden death". There were no deaths from these causes in any of the comparison groups. This occurred despite of restricting inclusion of patients with cardiovascular conditions in the trials.

Hypotension and orthostatic reactions

Lowered blood pressure is a prominent adverse effect, requiring a slow up-titration of the dose. In the placebo-controlled studies a systolic blood pressure ≤90 mm Hg and a decrease of ≥10 mm Hg was seen in 18.2% in the iloperidone combined group, compared with 7.1% in the placebo group and ranging between 8.7-16.9% in active comparator groups. The relation with iloperidone dose was inverse, with highest proportion of 23.4% seen in the low-dose (4-8 mg/d) group. This may be a consequence of patients failing to tolerate an up-titration of the dose.

A similar pattern was seen for diastolic blood pressure, where a diastolic blood pressure ≤65 mm Hg and a decrease of ≥10 mm Hg was seen in 52.9% in the iloperidone combined group, compared with 34.9% in the placebo group and ranging between 30.2-44.9% in active comparator groups. The relation with iloperidone dose was also here inverse.

There is a remaining high proportion with hypotension also during the open-label extension phase, suggesting that this problem is not restricted to the titration phase.

Other adverse effects potentially related to long-term cardiovascular safety

Cardiac AEs of mild or moderate severity occurred in 6.8% of patients in the combined iloperidone group in the overall safety population, which was higher than in any of the placebo (2.8%), haloperidol (2.9%), risperidone (1.9%), and ziprasidone (3.8%) groups. Serious cardiac AEs occurred in 0.4% both in the placebo and the iloperidone group. Of the 329 iloperidone-treated patients who had a cardiac AE, 30 (9.1%) had a dose reduction/interruption and 50 (15.2%) prematurely withdrew. One placebo-treated and 3 iloperidone-treated patients died of a cardiac-related event (2 considered sudden).

There are several adverse events that collectively may have a negative impact on long-term cardiovascular risk. Increased heart rate, fluid retention, increased blood lipids, increased serum uric acid, increased serum creatinine, and hyperglycaemia are all factors that appear related to treatment with iloperidone and are considered linked to cardiovascular risk. While some of these are expected class effects of antipsychotics, there are some notable observations. The effect of iloperidone on heart

rate appear to stronger compared to other antipsychotics. Any potential combined effect of these factors on long-term cardiovascular safety remains uncharacterised.

Extrapyramidal symptoms

In the overall safety population 0.9% of patients in the combined iloperidone group experienced an extrapyramidal disorder adverse event compared with 0.5% of placebo-treated patients. However, the incidence of extrapyramidal disorder in the combined iloperidone group was lower than in the haloperidol (1.6%), risperidone (1.3%) and ziprasidone (7.1%) groups. Treatment with iloperidone is associated with slightly more akathisia when compared with placebo, but less when compared with ziprasidone and risperidone, and notably less than haloperidol. No pooled analysis has been presented with data on the Extrapyramidal Symptoms Rating Scale (ESRS).

3.5. Uncertainties and limitations about unfavourable effects

Safety database

While the integrated safety database contains more than 4800 patients exposed to iloperidone only 12 out of 40 studies have been included. Only 171 patients received a dose of 20-24 mg/d for >6 months and 80 patients for >12 months. There are no subjects >69 years of age included in the studies presented. Roughly 1/3 of the patients were female. This means that there is remaining uncertainty regarding long-term safety. Since women are underrepresented and e.g. more prone to important adverse reactions such as QT prolongation, this means that overall frequencies of adverse reactions may be underestimated. No meaningful further characterisation has been submitted based on post marketing data despite of substantial post marketing exposure. The safety database is essentially identical to the approximately 4500 patients assessed in the previous application.

QT prolongation

It has been clearly established that the main safety concern is the risk for QT prolongation, and that there is a need to reduce the dose in patients who are at risk of increased exposure, e g for CYP2D6 poor metabolisers and due to drug-drug interactions. The suggestion to reduce the posology in CYP2D6 poor metaboliser patients by half is in line with available data. The dosing recommendations in case of concomitant use with interacting drugs have, however, not been adequately justified, in particular in case of combined use of strong inhibitors or with treatment of poor metabolisers with strong CYP3A4 inhibitors.

Genotyping is considered necessary but is not generally used, may be problematic to implement in the target population and was also not proposed by the applicant . There is a major concern that poor metabolizers will go undetected prior to dosing and will have a drug exposure significantly higher than extensive metabolizers, which may be linked to considerable safety concerns.

Iloperidone dose (within therapeutic range) did not appear to be clearly predictive of QTc prolongation. While the risk for QTc prolongation is related to concentration, this still raises a concern for the effectiveness of reduced iloperidone dose as a risk minimisation measure.

The actual impact on QTc may also be underestimated in the TQT study. The design of the TQT study unfortunately included no placebo arm. ECG measurements were not conducted over a dosing interval which hampers an analysis of non-linearity or a delay between peak plasma concentration and QT-prolongation. It is important to note that the C_{max} of Iloperidone and P88 following 12 mg BID at steady state in patients is expected to be approximately 32 and 37 ng/ml respectively (dedicated dose-proportionality study *Study ILO5220112* with rich sampling). C_{max} of Iloperidone and P88 in period 1 in the TQT study with 12 mg BID was only 21 and 24 ng/mL respectively. Furthermore, time-matched

concentration-QT_cF for measurements at 4 hours including all three treatment periods (which is the expected T_{max} for the active metabolite P88) were not presented. These two important caveats regarding the available TQT study data raise further concerns that the risk may not be sufficiently characterized.

The results from the TQT study support that iloperidone and the active metabolite P88 adversely affects the QT interval to a degree at least comparable to that of ziprasidone. The study may not have captured the full extent of adverse impact on the QT interval. Women had a stronger effect on the QT interval and were also underrepresented (30%) in the TQT study. This is a limitation and raises concern since women are expected to have longer QT and also be more sensitive to QT prolongation.

Yet another reason for why the available study data can have underestimated the risks associated with QTc prolongation is that in the major clinical trials, patients with prevalent cardiovascular disease and older adults were excluded and hospitalisation for 4 weeks was mandated in the key trial 3101. These are strong risk mitigation measures that are not relevantly reflected in the proposed risk minimisation measures and can lead to underestimation of these safety concerns.

The ultimate concern with QTc interval prolongation is related to the risk for fatal arrythmias. There were sudden deaths and cardiac deaths observed among those exposed to iloperidone in the clinical trials. Few patients were, however, studied long-term with the highest dose in the integrated safety data and no reassurance can be provided from post marketing data that is based solely on spontaneous reporting.

There is consequently a major concern regarding the risks associated with QT prolongation and the full clinical consequences cannot be predicted with available data, that likely underestimate the risks in clinical practice.

Long-term cardiovascular safety

There are several adverse reactions identified that all also are established risk factors for long-term cardiovascular morbidity and mortality. Increased heart rate, fluid retention, increased creatinine, increased uric acid, and increased blood lipids are all such risk factors. This has not been acknowledged by the applicant and adds to the uncertainty regarding long-term cardiovascular safety.

3.6. Effects Table

Table 40: Effects Table for iloperidone in the treatment of schizophrenia in adults

Effect	Short Description	Unit	Ilo	Active control	Pbo	Uncertainties/ Strength of evidence	References
	Favourable Effects						
BPRS total score	Reduction of psychotic symptoms from baseline to end of study	Mean change in total score (SD)	10-16 mg/d: −7.6 (12.6)	−11.1[a] (13.6)	−2.7 (14.3)	Mean change in treatment groups < MCID for BPRS. Slow onset of effect. P=0.001 vs pbo	Study 3004
			4-8 mg/d: −6.7 (12.4)			Mean change in treatment groups < MCID for BPRS. Slow onset of effect. P=0.12 vs pbo	Study 3004
PANSS total score	Reduction of psychotic symptoms from	Mean change in total	−12.01 (1.03)	−12.27[b] (1.44)	−7.08 (1.48)	Mean change in treatment group < MCID for PANSS.	Study 3101

Effect	Short Description	Unit	Ilo	Active control	Pbo	Uncertainties/ Strength of evidence	References
	baseline to end of study	score (SE)				Slow onset of effect. P< 0.01 vs Pbo.	
Time to relapse/ impending relapse	Time from randomisation to relapse/ impending relapse	Mean time, days	8, 12, 16, 20 or 24 mg/day: 139	N/A	71	P<0.0001 vs Pbo. HR (95% CI) 4.7 (2.7, 8.3)	Study 2301
	Unfavourable Effects [c]						
QTc ≥450 msec, females	Outlier analysis, ILO 20-24 mg/d	n (%)	69 (21.1)	4 (8.7)[b]	20 (6.0)	May not have been measured at C_{max}	
QTc ≥450 msec, males	Outlier analysis, ILO 20-24 mg/d	n (%)	69 (6.0)	0[b]	7 (1.2)	May not have been measured at C_{max}	
Cardiac Disorders AE	ILO combined	n (%)	329 (6.8)	7 (3.8)[b]	26 (2.8)		
Psychiatric adverse events	ILO combined	n (%)	543 (11.2)	2 (1.1)[b]	42 (4.4)		

Abbreviations: Ilo: iloperidone. Pbo: placebo. BPRS: 18-item PANSS-derived Brief Psychiatric Rating Scale. PANSS: Positive and Negative Syndrome Scale. MCID: Minimal clinically important difference. QTc: corrected QT value. AE: adverse events
Notes: [a] Risperidone; [b] Ziprasidone; [c] Safety population (Study Group 1)
Assessment comment: short-term studies 3000 and 3005 were negative.

Table 41: Effects Table for iloperidone in the acute treatment of manic or mixed episodes associated with bipolar I disorder in adults

Effect	Short Description	Unit	Ilo	Pbo	Uncertainties/ Strength of evidence	References
Favourable Effects						
YMRS total score	Reduction of manic symptoms from baseline to end of study	Mean change in total score (SE)	-14.0 (0.64)	-10.0 (0.63)	Modest magnitude of effect size. Slow time to onset of effect. P=0.000008	Study 3201
	Response defined as ≥50% reduction in YMRS Total Score at day 28	Proportion of participants, %	43.4%	33.5%	nominal p-value 0.0248	
CGI-S	Change in overall illness severity, day 21		-1.2 (0.08)	-0.9 (0.08)	nominal p-value 0.0146	
	Change in overall illness severity, day 28		-1.5 (0.08)	-1.1 (0.08)	nominal p-value 0.0005	
Unfavourable Effects [a]						
QTc ≥450 msec, females	Outlier analysis, ILO 20-24 mg/d	n (%)	69 (21.1)	4 (8.7)[b]	May not have been measured at C_{max}	
QTc ≥450 msec, males	Outlier analysis, ILO 20-24 mg/d	n (%)	69 (6.0)	0[b]	May not have been measured at C_{max}	

Effect	Short Description	Unit	Ilo	Pbo	Uncertainties/ Strength of evidence	References
Cardiac Disorders AE	ILO combined	n (%)	329 (6.8)	7 (3.8)[b]		
Psychiatric adverse events	ILO combined	n (%)	70 (4.5)	2 (1.3)[b]		

Abbreviations: Ilo: iloperidone. Pbo: placebo. YMRS: Young-Ziegler mania rating scale. QTc: corrected QT value. AE: adverse events.
Notes: [a] Safety population (Study Group 1); [b] Ziprasidone

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Schizophrenia, favourable effects

Psychotic disorders affect approximately 1.2 % of the worldwide and EU populations. Schizophrenia is a progressive and recurring disorder characterized by multiple psychotic relapses and potential functional decline over time. The societal implications are important, both in terms of direct healthcare costs and in terms of indirect costs, including productivity losses and caregiver burden. Antipsychotic agents (dopamine receptor antagonists/partial agonists) are the standard of care, preferably combined with non-pharmacological treatment approaches. Although many treatment options exist, there is an unmet medical need as treatment discontinuation is very common, because of actual or perceived lack of effect, side effects, and limited patient understanding of their condition.

The objectives of therapy in schizophrenia are to shorten the duration of an acute psychotic exacerbation, to prevent relapse and to improve overall level of functioning. Since an acute psychosis can be associated with suffering and different kinds of risks to the patient and others, time to onset of effect is an important part of treatment efficacy.

Treatment efficacy is usually measured with a standardised interview assessing positive, negative and general symptoms associated with schizophrenia. The PANSS or the 18-item PANSS-derived BPRS are commonly used. Both change from baseline to end of study and change from treatment visit to treatment visit are important aspects of this measure, as well as treatment response defined as a reduction of the total score by at least 20%, 30% or 40%.

Iloperidone has been studied in several short-term studies and one randomised withdrawal study. However, only 2 out of the 4 short-term trials in schizophrenia showed a statistically significant effect in the primary analysis, and these results were no longer statistically significant when missing data were handled using a reasonably conservative imputation method. According to literature, the magnitude of the effect in all short-term studies falls below the minimum clinically important difference (MCID)[4] for the assessment instrument used[5]. In addition, there were numerical differences with respect to the magnitude of the effect and the time to onset of effect (observed between 1.5-3 weeks

[4] Defined as "the smallest difference in a score in the domain of interest which patients [or providers] perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a meaningful change in the patient's management." *Jaeschke, R., et al. (1989)*. "Measurement of health status. Ascertaining the minimal clinically important difference." Control Clin Trials 10(4): 407-415.
[5] PANSS: between a 19% and 34% change in PANSS total score; *Hermes, E. D., et al. (2012).* "Minimum clinically important difference in the Positive and Negative Syndrome Scale with data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)." J Clin Psychiatry 73(4): 526-532.
BPRS: a percentage reduction of the BPRS by approximately 28 percentage points reflected a reduction of the CGI severity score by one severity step, and a 10-points reduction corresponded roughly to minimal improvement. *Leucht, S., et al. (2006).* "Linking the PANSS, BPRS, and CGI: clinical implications." Neuropsychopharmacology 31(10): 2318-2325.

later) not favouring iloperidone in comparison to the active comparators (ziprasidone, risperidone and haloperidol) included in the short-term studies.

In the relapse prevention study, iloperidone treatment in patients who were stabilised on iloperidone reduced the risk of relapse compared with placebo treatment. The proportion of patients relapsing on iloperidone treatment during this study was similar to what has been observed with other antipsychotic agents.

Bipolar disorder, favourable effects

Bipolar disorder affects approximately 1-2% of the worldwide and EU populations. Bipolar I disorder is characterized by recurrent manic, mixed and depressive episodes, with significant impact on functioning over time. Full recovery without further episodes is rare, with recurrence and incomplete remission being the rule. For the acute treatment of manic or mixed episodes, lithium, antipsychotics and mood stabilisers are the standard of care. Pharmacological treatment shortens the duration of manic/mixed/depressive episodes and lessens the risk of relapse.

There is an unmet medical need as treatment discontinuation is very common, because of actual or perceived lack of effect, side effects and lack of insight in the nature of the disorder and the risk of relapse.

Treatment efficacy is usually measured with the YMRS, a standardised interview assessing symptoms of mania. Both change from baseline to end of study and change from treatment visit to treatment visit are important aspects of this measure, as well as treatment response defined as a reduction of the total score by at least 50%. The MADRS can be used to assess depressive symptoms both as part of a mixed episode, and to assess switch from a manic to a depressive state during treatment of mania. As an acute manic or mixed episode can be associated with suffering and different kinds of risks to the patient and others, time to onset of effect is an important part of treatment efficacy. Further, both the current EMA guideline (CPMP/EWP/567/98) and its 2024 draft revision (EMA/CHMP/406037/2024 rev. 1) states that maintenance of effect during an episode has to be shown also in mere acute treatment claims. A total study duration of 12 weeks is recommended in both versions of the guideline, with the draft revision giving more detailed advice ("*For mania, maintenance of effect during the episode has to be shown. A placebo control during this period will be difficult. Therefore, an active comparator is acceptable, provided that assay sensitivity is taken into account. A possible design is a comparison of placebo, test product and active control for three weeks followed by a two-arm phase for the remaining nine weeks, comparing only test product and active control.*").

Acknowledging the statistically significant difference in symptom reduction compared to placebo after four weeks of treatment, the magnitude of the effect of iloperidone treatment compared to placebo could be considered as modest, with an average reduction of 3.2 points on the YMRS. Further, there are concerns about the delayed onset of effect of iloperidone, where a nominally significant but clinically not relevant separation from the placebo group occurs first at day 14, potentially due to the need for slow up titration of the dose**.** Maintenance of effect during the episode has not been studied, rendering this important aspect of acute treatment insufficiently characterised.

There were no indications that iloperidone treatment caused a switch from a manic or mixed state to a depressive state during the short-term study, but long-term data is missing.

Unfavourable effects

QT prolongation

It is essential to acknowledge the magnitude of iloperidones effect on the QTc interval, the severity of associated risks in long-term use in clinical practice, the added concerns related to the complicated metabolism of iloperidone, and the low feasibility of sufficient risk minimisation ranging from

genotyping to control of other external risk factors for QTc prolongation throughout a prolonged treatment period.

Relevant guidance regarding regulatory consequences is provided in the ICH E14 Guideline:

> *"Substantial prolongation of the QT/QTc interval, with or without documented arrhythmias, could be the basis for non-approval of a drug or discontinuation of its clinical development, particularly when the drug has no clear advantage over available therapy and available therapy appears to meet the needs of most patients. Failure to perform an adequate clinical assessment of the potential QT/QTc interval prolonging properties of a drug can likewise be justification to delay or deny marketing authorization. For non-antiarrhythmic drugs, the outcome of the risk benefit assessment will generally be influenced by the size of the QT/QTc interval prolongation effect, whether the effect occurs in most patients or only in certain defined outliers, the overall benefit of the drug, and the utility and feasibility of risk management options. The inclusion of precautionary material in the prescribing information will not necessarily be considered an adequate risk management strategy, if implementation of the recommendations in a clinical use setting is judged to be unlikely. If QT/QTc interval prolongation is a feature shared by other drugs of the therapeutic class in question, evaluation of the new drug could usefully involve a comparison of the magnitude and incidence of any QT/QTc interval prolongation effects relative to those of other members of its class in concurrent positive control groups.*
> */…/*
> *Regardless of the degree to which a drug prolongs the QT/QTc interval, decisions about its development and approval will depend upon the morbidity and mortality associated with the untreated disease or disorder and the demonstrated clinical benefits of the drug, especially as they compare with available therapeutic modalities. Demonstrated benefits of the drug in resistant populations or in patients who are intolerant of, or have a labelled contraindication to, approved drugs for the same disease represent additional relevant clinical considerations that might justify approval of the drug, if the indication were limited to use in such patients."*

It is consequently clear that the concerns regarding QTc prolongation have a substantial adverse impact in the overall benefit-risk balance.

This risk is not predictable, nor limited to the treatment initiation phase. The magnitude of the risks raises a major concern in and by itself but is further aggravated by the complication that the metabolism of iloperidone and its active metabolite P88 is highly dependent on CYP2D6 and also on CYP3A4. This can lead to additional risks for patients with poor metabolizer CYP2D6 genotype and/or patients taking other medications inhibiting these enzymes.

While the proposed risk minimisation measures are rudimentary and clearly insufficient, it is also very difficult to see how improved risk minimisation would be able to substantially reduce this concern, considering the feasibility of adequate risk minimisation in a clinical practice context.

Other unfavourable effects

The effect on blood pressure, where orthostatic hypotension mandates a slow up-titration of the dose, is of importance not only from the direct adverse reactions but also contributing to the slow onset of a relevant clinical effect due the titration procedure.

The potential effects on long-term cardiovascular safety, from risk factors other than the QT interval prolongation, is an important concern since long-term treatment is often required. This risk is, however, insufficiently characterised but must be considered in the overall benefit-risk evaluation.

There may be a benefit of iloperidone in terms of lower incidence of extrapyramidal symptoms but based on the data presented uncertainty regarding the actual magnitude of this potential benefit remains.

3.7.2. Balance of benefits and risks

3.7.2.1. Schizophrenia

The results of the short-term studies in patients with schizophrenia are not considered as statistically robust. In addition, the magnitude of the effect is potentially lower compared to comparators included in the pivotal studies. Further, there are concerns about the delayed onset of effect, potentially due to the need for slow up-titration of the dose.

At the same time iloperidone is associated with a substantial risk of prolongation of the QT interval with an associated clear risk for potentially fatal arrythmias. The risk is not predictable, nor is it limited to treatment initiation. The magnitude of these adverse effects by itself raises a major concern, that is further aggravated by the complicated dependence on metabolism and genetic and other risk factors. The overall benefit-risk relation is therefore negative.

A feasible and effective risk minimisation strategy has not been identified, such that this could render the limited beneficial effects outweigh the major safety concerns identified.

Based on these considerations the benefits are not considered to outweigh the risks.

3.7.2.2. Bipolar disorder, acute mania or mixed episode

The magnitude of the observed effect of iloperidone in the treatment of bipolar disorder may be considered as limited. Further, it is a concern that there is a lack of data beyond 4 weeks of treatment as well as concerns about the delayed onset of effect potentially due to the need for slow up-titration of the dose. At the same time iloperidone is associated with a substantial risk of prolongation of the QT interval with an associated clear risk for potentially fatal arrythmias. The risk is not predictable, nor is it limited to treatment initiation. The magnitude of these adverse effects by itself raises a major concern, that is further aggravated by the complicated dependence on metabolism and genetic and other risk factors. The overall benefit-risk balance is therefore negative.

A feasible and effective risk minimisation strategy has not been identified, such that this could render the limited beneficial effects outweigh the major safety concerns identified.

Based on these considerations the benefits are not considered to outweigh the risks.

3.7.3. Additional considerations on the benefit-risk balance

Only small number of older patients (≥65 years) have been included in the clinical studies for the indications applied for. Considering that iloperidone causes QT prolongation, which increases risk for potentially fatal arrhythmias, and hypotension, the safety in older patients has not been appropriately analysed and established. Not only that these adverse events may be more pronounced in the elderly patients, but they add risk to the other cardiovascular risk factors already more frequently present in older patients. Data from submitted short-term studies ILP3007 Part 1 and ILP3007 Part 2 (treating psychotic and behavioural symptoms in elderly patients with dementia) do not allow such analysis also because doses used were significantly lower (most of patients received up to 2 mg/day) than doses recommended in the product information for sought indications (up to 24 mg/day).

3.8. Conclusions

The overall benefit/risk balance of Iloperidone Vanda Pharmaceuticals is negative.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy for Iloperidone Vanda Pharmaceuticals in the treatment of schizophrenia in adults and acute treatment of manic or mixed episodes associated with bipolar I disorder in adults, the CHMP considers by consensus that the safety and efficacy 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:

- Treatment with iloperidone is associated with pronounced prolongation of the QT interval and a risk for potentially fatal arrythmias which is not considered to be outweighed by the benefits of treatment. A feasible and effective risk minimisation strategy to identify and monitor patients at increased risk for potentially fatal arrhythmias has not been identified and therefore the risk cannot be sufficiently mitigated.
- In patients with schizophrenia, this risk is not considered outweighed by the observed treatment effect since the results from the short-term studies are not considered statistically robust in light of the results of performed sensitivity analyses. In addition, there are concerns about the delayed onset of effect, potentially due to the need for slow uptitration of the dose.
- In patients with acute manic or mixed episodes associated with bipolar I disorder, this risk is not considered outweighed by the observed effect in the short-term treatment study, the lack of controlled data beyond 4 weeks of treatment as well as the delayed onset of effect, potentially due to the need for slow uptitration of the dose.

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling, package leaflet, pharmacovigilance system, risk management plan and post-authorisation measures to address outstanding other concerns cannot be agreed at this stage.

Furthermore, following review of the available data in the context of the applicant’s claim of new active substance status, the CHMP position is reflected in the respective Appendix.